ACTA RADIOLOGICA
EDITA IUSSU SOCIETATUM RADIOLOGICARUM
DANIAE, FENNIAE, NORVEGIAE ET SUECIAE

VOL. 48 NOVEMBER 1957 FASC. 5

ARTERIOGRAPHY IN BRACHIOCEPHALIC ARTERITIS (PULSELESS DISEASE OR THE TAKAYASHU SYNDROME)

by

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The condition to be discussed appears in the literature under various names. It is called the 'pulseless disease' from the sign which is most easy to elicit, viz. the more or less complete disappearance of a palpable pulse in one, or more frequently in several arteries. The phenomenon is practically always confined to the brachial artery or to the common carotid artery and the branches of these vessels. The symptoms and signs are therefore often connected with ischemia in the regions which these vessels supply and may consist of intermittent claudication in the arms and the musculature of the jaw, visual disturbances, transitory hemiplegia or aphasia, tendency to fainting, etc., caused by a more or less marked constriction of the ascending branches of the aortic arch. The obliteration is usually confined to the first parts of the vessels, but it may extend as far as the axillary artery or up into the carotid arteries at the base of the skull. In advanced cases changes may occur also in the thoracic part of the aorta; they have even been described in the abdominal aorta and its branches.

Submitted for publication 3 May 1957.

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Changes in the arteries of the lower extremities seem to have been reported, as far as I have been able to ascertain, only by ASK-UPMARK who in a case with typical symptoms and signs found severe inflammatory changes even in the dorsalis pedis artery. The constriction appears to be in the nature of an inflammatory process, with cell infiltration in all the layers of the arterial wall. Giant cells may also occur.

The patho-anatomic changes resemble those occurring in other types of arteritis, such as temporal arteritis and endo-arteritis obliterans. But the 'pulseless' disease differs from these conditions not only in its situation and by almost always affecting young or middle-aged women, but also in that the condition is a progressive one. The prognosis is consequently less favourable.

The etiology is not known with certainty but many factors seem to indicate that the process is of a 'rheumatic' character. A conspicuous feature is a previous history of manifestations of rheumatic disorders. The sedimentation rate is mostly augmented, in many cases to values exceeding 100 mm/hr. A murmur, usually of the 'typewriter' variety, is often heard over the constriction.

The disease seems to have been described for the first time by the Japanese ophthalmologist TAKAYASHU. It is therefore also termed the TAKAYASHU syndrome, and a fairly large number of cases have been described in Japan. The Americans CACCAMISE and WHITMAN, who reported a case in 1952, stated that at that time 58 cases had been recorded in the Japanese literature; they believed their own case to be the first one observed outside Japan. That this is not true has been shown by ASK-UPMARK in a large survey of the disease, published in 1954. In this report, 28 cases observed elsewhere than in Japan were collected; none of these had been previously published and two had been observed by the author. In an addendum, ASK-UPMARK mentions two further cases in which the diagnosis was considered somewhat uncertain mainly because the charges were not observed in the usual situations. In one of these latter cases, which was observed by LUBLIN at Gävle (Sweden), the change was confined to the axillary artery, and in the second case which was examined by ASK-UPMARK the charge was localized to the carotid artery.

That CACCAMISE and WHITMAN erroneously believed their own case to be the first one observed in a country other than Japan may at least in part have been due to the fact that the disease is apparently not very widely known, and as a result has been described in the literature under different names. Neither HARBITZ and RAEDER nor FRÖVIG and LÖKEN, for instance, seem to have had any knowledge of the article published by TAKAYASHU.

After 1946, when LINDQUIST reported 2 cases in Gothenburg, attention had been directed towards the comparatively unusual clinical picture of the disease. In recent years therefore, a number of cases have been diagnosed in this neighbourhood. Of the cases included in the report by ASK-UPMARK, 3 had been observed by RUDBÄCK and WELIN in 1953; WELIN subsequently had 2 further cases in the hospital of Mölndal (near Gothenburg), and upon which the present author had the opportunity of carrying out argiographies — these were described at the conference of the Scandinavian Society for medical radiology in Gothenburg 1955.

In advanced cases, the clinical signs are characteristic and therefore sufficient for establishing a definite diagnosis. It seems probable, however, that as the symptomatology becomes more widely known the diagnosis will not only be more frequently established but the disease will also probably be suspected at an earlier stage; it will not then be possible to arrive at a definite diagnosis from the clinical signs alone.

Biopsy used to be the most common method for verifying the diagnosis in vivo although the vascular region which is primarily involved is also as a rule comparatively difficult of access. Oscillometry and skin temperature measurements may indirectly serve to demonstrate a vascular occlusion, but these methods do not permit any assessment of its detailed appearance, nor of its nature and site.

On the other hand, it is possible by means of arteriography to establish not only the location, extent, and degree of the changes, but also their type. Information about the existence of a collateral circulation may also be obtained, as well as general data about the circulation in the vascular areas affected. By repeating the examination at intervals there is moreover the possibility of following the progress of the disease and so observing the effects of treatment.

Arteriography post mortem has been advocated by FRÖVIG and LÖKEN inter alios. These authors succeeded in mapping out the extent of the changes by arteriography, and they also demonstrated a collateral circulation, mainly through dilated intercostal arteries. These arteries had even caused notching of the ribs of a type earlier considered characteristic of coarctation of the aorta. Arteriography in vivo, on the other hand, has been mentioned by ASK-UPMARK in two atypical cases briefly referred to in an addendum to his report, and by ADAMSON, LINDGREN and LUND, who described the arteriographic findings in two cases. The latter paper is, however, in Swedish and no illustrations were shown.

Under these circumstances I feel justified in publishing a brief description, together with a short discussion mainly of the roentgenographic changes in the two cases which I examined. The reader who is interested

a b c

Fig. 1. Case 1. Constriction of the popliteal artery which gradually diminishes in both directions; arterial walls regular and smooth. b) and c) After 4 year's cortisone treatment. Constriction now rather less marked.

in a more detailed account of the clinical aspects is referred to the article by ASK-UPMARK, and to an article by WELIN which will be published later.

Author's cases

Case 1. Woman, aged 47 years, with joint disorders of a rheumatic character for 4 years, and cramp-like pain in the chest wall radiating towards the shoulders for 3 years. The symptoms gradually increased, and during the previous 6 months she experienced loss of power in the left arm as well as an intermittent claudication type of cramp in the right lower leg. On examination (WELIN) it was established that the left radial pulse was weaker than the right. Blood pressure: Left arm, 120/110; Right arm, 160/90. Systolic thrill present as well as a systolic murmur extending along the carotid artery. Oscillometry showed a greatly reduced amplitude of reaction in the right lower leg and left arm. S. R. 42 mm/hr.

Angiography was performed via the right femoral artery (Fig. 1) as well as via the left subclavian artery. In the latter examination, an attempt was first made to introduce the catheter through the brachial artery. As this did not succeed, the catheter was inserted

Fig. 2. Case 1. Fairly marked constriction of subclavian artery similar to that seen in popliteal artery. Catheter introduced via femoral artery, the tip being placed at the point of origin of subclavian artery.

through the femoral artery, the tip being placed at the point of origin of the subclavian artery (Fig. 2). Constrictions of the lumina of the proximal portion of the subclavian artery and of the popliteal artery were evident; in the latter situation the constriction diminished gradually. The vascular walls were smooth and regular in the constricted regions. No collateral circulation could be detected. A considerable amelioration seemed to have been attained after treatment with cortisone; not only were the symptoms less severe, but the oscillometric changes almost completely disappeared and the radial pulses were practically equal. On examination 4 years later (Fig. 1 b and c) the constriction of the popliteal artery was seen to be rather less marked.

Case 2. Woman, 57 years old, who for many years had suffered from joint disorders of a rheumatic type. She had lately felt tired, and experienced giddiness, headache, and repeated attacks of fainting, without completely losing consciousness. She had known for at least 5 years that her radial pulses were absent. On examination (WELIN): Radial pulses not palpable. No pulse from left carotid artery. A systolic murmur was heard in the left supraclavicular fossa, radiating out into the left arm. S. R. 41 mm/hr.

Angiography. Angiography was again performed by introducing a catheter via the femoral artery, since an attempt to puncture the brachial artery failed due to the feeble pulsations. An injection was first made with the tip of the catheter placed at the origin of the brachiocephalic trunk. The position of the catheter was then changed so that the tip lay approximately at the origin of the left subclavian artery.

On the right side (Fig. 3, top view) there was a wide vessel with a course corresponding approximately to that of the brachiocephalic trunk. It merged smoothly into the carotid artery which was wider than normal. No contrast filling of the proximal portion of the

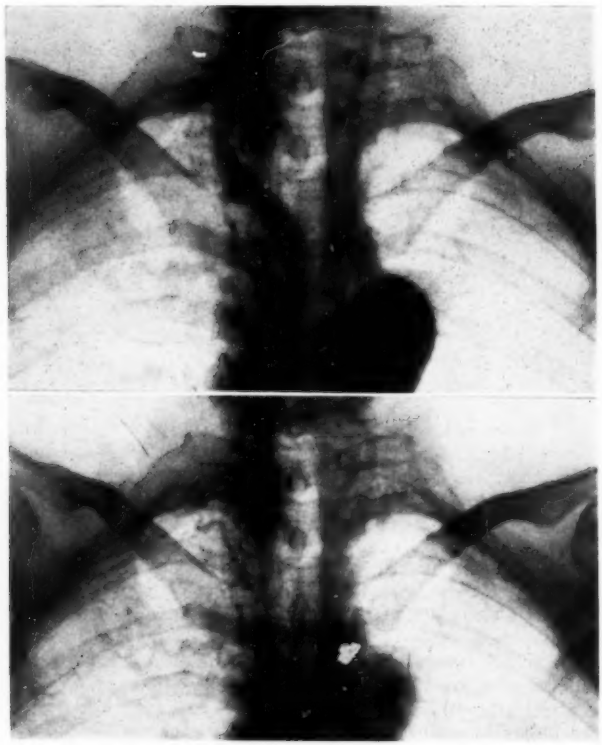

Fig. 3. Case 2. Brachiocephalic trunk of large size merges smoothly into the wide carotid artery. Proximal part of right subclavian artery not outlined, the distal part being filled in a later phase (bottom view) by way of a collateral circulation. Narrowed collaterals also on left side. Left subclavian artery appears to be partly patent in its proximal part. (The left subclavian and carotid arteries were later filled with a higher concentration of contrast medium with tip of catheter near the point of origin of these vessels.)

subclavian artery was obtained, but the peripheral part was contrast filled, apparently by way of a collateral circulation. This circulation was composed of the dilated intercostal arteries and of a branch from the subclavian artery anastomosing with the first intercostal artery. On the left side, the subclavian as well as the carotid artery were very narrow; the intercostal arteries on this side were dilated but not to the same extent as on the right (Fig. 3, bottom view).

Discussion

The contrast media used for angiographies — complex iodium compounds of the Diodrast, Urokon or Hypaque type — may give rise to complications, at least if employed in large amounts or too high concentrations. In order to obtain satisfactory films with the least possible quantity and concentration of contrast medium, the injection should be performed as near as possible to the vascular region to be examined. This is particularly important in those cases in which the cerebral vessels will also become contrast filled, the brain being particularly sensitive to the compounds mentioned.

It is as a rule diffcult, and moreover not entirely free from risk to make the puncture directly into the ascending branches at their origins from the aortic arch. For an examination of these vessels, therefore, the most appropriate method is to inject the contrast medium through a catheter introduced in such a way that the tip can be placed near the point where the vessel arises from the aorta. I use Seldinger's method. A flexible metal guide is introduced into the vessel through the puncture needle, and the latter is withdrawn; a plastic catheter is then inserted around the guide which is also withdrawn.

If the catheter can be introduced into the vessel to be examined, this constitutes the easiest method. The pulsations of the vessel may be so weak, however, as to make this impossible. If this procedure should also fail, an effort should be made to place the catheter in the aortic arch as near the actual branch as possible.

To make certain that at least the major part of the contrast medium will pass through the vessel under examination, a trial exposure after the injection of a small amount of contrast medium should be made. If it is then found that the catheter is in the correct position, 15 to 20 ml Urokon (type) 40 % will suffice for the completion of the examination.

By injecting a greater quantity of contrast medium of high concentration, it is of course possible to obtain filling of the aortic arch as well as its branches from one and the same injection. The risk that the concentration in the cerebral vessels will be too high will then be increased as will also the risk of complications. Untoward sequelae from this cause have been reported in connection with angiocardiographies and thoracic aortographies.

The changes noted in the cases presented differ from those seen in arteriosclerosis by the regular nature of the constriction and the smooth walls within the occluded region (Fig. 4). In my experience, a regular constriction is not a feature of endo-arteritis obliterans, and even if the changes occur at a site of election for endo-arteritis obliterans, as happened

Fig. 4. Right subclavian artery partly constricted just distal to its origin from the brachiocephalic trunk. The constriction is much shorter than in the other and somewhat irregular; it proved to be caused by arteriosclerosis.

in the first of the cases, there appears to be a reasonable chance of establishing a differential diagnosis between these two conditions by means of arteriography.

SUMMARY

The signs and symptoms of brachiocephalic arteritis, pulseless disease, or TAKAYASHU syndrome, are briefly described; the changes in two cases observed at angiography with special reference to the technique and the value of the procedure are discussed.

ZUSAMMENFASSUNG

Die Symptome der brachiocephalen Arteriitis, der pulslosen Krankheit oder des TAKAYASHU-syndromes werden kurz beschrieben. Die Veränderungen, die in 2 Fällen bei Angiographien beobachtet wurden, werden mit besonderer Berücksichtigung der Technik und des Wertes dieser Prozedur diskutiert.

RÉSUMÉ

L'auteur décrit brièvement les signes physiques et fonctionnels de l'artérite brachiocéphalique, maladie sans pouls ou syndrome de TAKAYASHU; il étudie les modifications angiographiques observées dans deux cas et insiste sur la technique et l'intérêt de cette méthode.

REFERENCES

Adamson, C. A., Lindgren, E. and Lund, F.: S. k. pulseless disease. (Swedish.) Nord. Med. 55 (1956), 489.

Ask-Upmark, E.: On the 'pulseless disease' outside of Japan. Acta med. scand. 149 (1954), 161.

Broman, T. and Olsson, O.: The tolerance of cerebral blood-vessels to contrast medium of the Diodrast group. Acta radiol. 30 (1948), 326.

— — Experimental study of contrast media for cerebral angiography with reference to possible injurious effects on the cerebral vessels. Acta radiol. 31 (1949), 321.

Caccamise, W. C. and Whitman, J. F.: Pulseless disease, a preliminary case report. Amer. Heart J. 44 (1952), 629.

Frövig, A.: Bilateral obliteration of the common carotid artery. Trombangitis obliterans? Acta psychiat. (Kbh.) Suppl. 39 (1946).

— and Löken, A.: Syndrome of obliteration of arterial branches of aortic arch, due to arteritis. Post-mortem angiographic and pathological study. Acta psychiat. (Kbh.) 26 (1951), 313.

Jönsson, G., Brodén, B. and Karnell, J.: Thoracic aortography. Acta radiol. Suppl. 89 (1951).

Lindquist, T.: Arterit i de från aortabågen utgående artärerna. (Swedish.) Nord. Med. 37 (1948), 321.

Ödman, P.: Percutaneous selective angiography of the main branches of the aorta. Acta radiol. 45 (1956), 1.

Raeder, J. G. and Harbitz, F.: Atrophy of face and eyes (presentic cataract and 'glaucoma' caused by symmetrical carotid affection). Norsk Mag. Laegevid. 87 (1926), 529.

Seldinger, S. I.: Catheter replacement of the needle in percutaneous arteriography. Acta radiol. 39 (1953), 368.

Takayashu, M.: Quoted by Ask-Upmark. Acta Soc. Ophth. Jap. 12 (1908), 554.

Trias de Bes, Lucas S. and Barcone, B.: A case of Takayashu's syndrome. The pulseless disease. Brit. Heart J. 17 (1955), 484.

Welin, G.: Arteritis brachiocephalis. To be published in Acta med. scand.

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OPERATIVE INTESTINAL ARTERIOGRAPHY

by

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The value of angiography has increasingly been emphasized during the past few years. The introduction of contrast substances into vascular channels has undoubtedly opened many new diagnostic avenues and allowed therapeutic procedures to be carried out with greater precision and increasing success. The majority of angiographic examinations are performed through the percutaneous route, either by direct puncture of the selected vessel or by advancing sometimes elaborate catheters under fluoroscopic guidance. The advantages of such non-surgical approaches are quite obvious. Yet, certain vascular territories remain relatively inaccessible by these conservative means.

In the following, the injection of radio-opaque material during surgery into arteries supplying certain areas of the intestinal tract will be discussed. This communication not only aims at the presentation of some of our observations but also intends to stimulate further interest in this rather simple and innocuous procedure which has been given the description of 'operative intestinal arteriography'.

Technique. The necessary precautionary tests against possible idiosyncrasies to the contrast medium and local anesthetic agent must be done prior to induction of anesthesia.

A portable Potter-Bucky diaphragm is put on the operating table, surrounded by a double layer of operating table mattresses and additionally covered with a sheet of foam rubber so as to avoid the possibility of pressure necrosis. A preliminary film is taken to verify the correct positioning of the patient.

Submitted for publication 15 April 1957.

Fig. 1.

Fig. 2.

Fig. 1. Injection of 15 ml of contrast substance into main trunk of inferior mesenteric artery. Superior hemorrhoidal artery and ascending branch of left colic artery occluded with clamps. Segmental filling of vessels along descending and sigmoid colon.

Fig. 2. Injection of 10 ml of Hypaque at identical level. Clamp on superior hemorrhoidal artery removed. Left colic artery still occluded, but vessels of upper rectum now filled with contrast medium; three areas of increased radio-opacity. Adjacent rectosigmoid appears uniform. Arrows point to line of abrupt cessation of blood supply furnished by superior hemorrhoidal artery.

The principal artery leading to the vascular territory to be injected, and preferably also its main ramifications, are dissected free at their origin over a distance of 2 to 3 cm. This, as well as the entire angiographic examination is best done prior to any mobilisation of the bowel. The wall of the main arterial trunk is punctured with a 17 gauge (diameter 0.145 cm) spinal needle and a plastic catheter (BD No. 444 T) introduced into the artery. The tip of the catheter must be located proximally to the origin of the first arterial ramification in order to allow contrast medium to flow into the various branches. The catheter may be held in position within the arterial lumen with a single knot ligature of heavy silk carried around the artery. The isolation of the various secondary branches will permit their temporary occlusion with small arterial clamps. By alternating the site of occlusion it is thus possible to fill selected vascular territories with contrast medium.

The contrast substance used in the present study was a 50 per cent solution of Hypaque (sodium 3,5 diacetamido-2,4,6 triiodobenzoate). (Hypaque was made available through the courtesy of the Research Department of Winthrop Laboratories Inc. New York, N. Y.) Vascular spasm can be minimized by the injection of 2 to 3 ml of 1 per cent

Procaine hydrochloride directly into the artery. The amount of contrast medium required for the adequate filling of a given vascular area averages between 10 and 15 ml, and the injection should be carried out as rapidly as possible. The exposure is made during the injection of the last 1 to 2 ml of the medium. A wet reading of the films is obtained, and if the results are considered satisfactory the catheter may be withdrawn. Adequate hemostasis is achieved by the application of oxydized cellulose to the site of arterial puncture.

Discussion

The normal angiographic appearances of the inferior mesenteric artery and its branches are illustrated in Figs. 1 to 4. The alternating temporary occlusion of secondary arteries greatly contributes to the quality of the examination. Hence, a picture superior in detail can be obtained with less contrast medium per injection by what may be called 'selective operative intestinal arteriography'. This fact can be appreciated by comparing Figs. 1 and 2, which represent roentgenograms of selected vascular territories, with Fig. 4, which corresponds to a film obtained after the injection of 30 ml of contrast medium into the main trunk of the inferior mesenteric artery but without occlusion of any of its branches. It thus appears that the additional few minutes required for the isolation of the various arterial branches are quite worthwhile.

The contrast medium is seen to outline the intestinal contour in a more or less uniform manner. This is accomplished either through unobstructed arteries or through collaterals in case of temporary arterial occlusion (Figs. 1, 2, 4). The degree of radio-opacity may show some variations from one segment to another depending upon the degree of local circulation, but nevertheless remains rather uniform. The haustrations, which anatomically correspond to areas of circular thickening of the intestinal wall, appear as regular bands of uniform density. However, localized areas of increased radio-opacity due to overlapping of loops of intestine cannot be completely avoided. This somewhat unfavorable factor can be minimized by limiting each injection to selected segments of intestine. Such separate injections reveal that the blood supply of the left colon is quite segmental in distribution. In some regions, a collateral circulation can be demonstrated, such as in the descending and sigmoid colon. In other areas, however, there appears to be no filling with contrast medium of intestinal segments supplied by a different arterial tree. This is clearly exemplified by the abrupt cessation of the arterial circulation in the lower recto-sigmoid (Fig. 2).

This arteriographic appearance of normal intestinal segments is different from the one observed in areas containing adenocarcinoma or polyps. This is readily seen by comparing the vascular details of the sigmoid colon adjacent to the recto-sigmoid (Figs. 2 and 3). The latter

Fig. 3. Close-up of angiographic pattern of upper rectum and lower sigmoid. Single arrows point toward 2 benign polyps. Individually increased blood supply of distal polyp. Double arrows point to fungating adenocarcinoma with central depression.

region contains a large circular area and two smaller foci of increased radio-opacity. These various areas correspond to a fungating adenocarcinoma with central depression and to two benign polyps, respectively (Fig. 5). Part of the arterial blood supply of the distal polyp appears to be furnished by several small vessels leading in a concentric fashion to the lesion. The arterial irrigation of the distal segments of the rectum is accomplished through the middle and inferior hemorrhoidal arteries which are not branches of the injected inferior mesenteric artery. Therefore, the observed collection of contrast medium in the mentioned localized area does not represent a cross section through a large vessel but must correspond to the focus of polypoid hypertrophy of the intestinal mucosa visible on the gross specimen. Thus, even very small polypoid formations are detectable by this method.

Based upon the histologic difference between the two types of lesions demonstrated, it must be emphasized that operative intestinal arteriography does not establish the correct pathologic diagnosis. The angiographic appearances appear to be linked to the degree of local vascularity rather than to the type of cellular composition. However, this method seems to be of value in determining the extent of a lesion and in

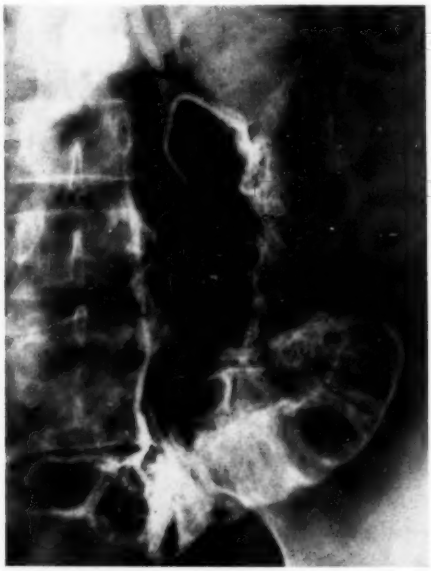

Fig. 4. Injection of 30 ml of Hypaque at identical level. All branches of the inferior mesenteric artery unobstructed. Vascular pattern less detailed and not demonstrated in upper rectum.

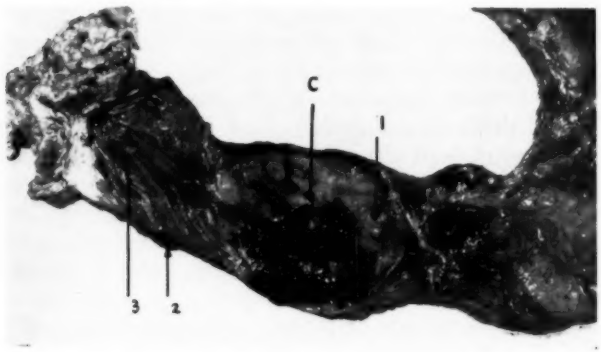

Fig. 5. Gross specimen from the patient. C = adenocarcinoma. 1 and 2 = benign adenomatous polyps demonstrated in arteriogram. 3 = polyp, not angiographically visible since located in lower rectum which received its blood supply from a different arterial tree (middle and inferior hemorrhoidal branches of hypogastric artery).

locating possible additional ones. A final evaluation of the full significance of operative intestinal arteriography must, however, await the accumulation of additional experience.

Several technical factors may represent certain limitations to the procedure. If an attempt is made to demonstrate the arterial, capillary and venous phase, respectively, three separate injections associated with concomitant roentgenographic exposure must be performed. The use of a seriograph would in this respect be ideal and would avoid the necessity of separate injections and haphazard estimation of the proper moment of roentgenographic exposure. However, no practical device of this type for adaptation on the operating table has been available in our department. Several otherwise satisfactory roentgenograms were lacking in sharp detail partly because of the difficulty in reducing intestinal peristalsis. The control of respiration during roentgenographic exposure may only occasionally represent a problem. Yet, it must be said that in spite of these somewhat limiting factors highly satisfactory arteriograms were obtained in the majority of instances.

Conclusions

The conclusions to be drawn from the present study are as follows:

1. Injections of contrast medium into selected arteries of the intestinal tract are not only feasible but also technically simple and rapidly executed.

2. Sterility is maintained throughout the entire procedure.

3. Operative intestinal arteriography is innocuous to the patient if precautions against idiosyncrasies to the contrast medium and local anesthetic agent are taken prior to induction of anesthesia. No immediate or late ill effects of any kind have been observed in the present series, especially no evidence of thrombosis. The bowel itself did, as verified during surgery up to five hours after injection, not show any evidence of distress, and the postoperative course was in no way affected by the procedure in any instance.

4. The vascular pattern of normal bowel is rather uniform, in contradistinction to the one observed in presence of lesions such as adenocarcinoma and polyps. These lesions are characterized by areas of increased radio-opacity, and in some instances appear to have an individually augmented blood supply.

5. The arteriogram reflects the vascularity of a lesion rather than its cellular composition.

6. Operative intestinal arteriography yields information as to the extent of a lesion and may be of value in detecting additional ones.

7. The collateral blood supply of intestinal segments can be evaluated.

SUMMARY

The authors describe a safe and technically simple angiographic method used in the course of abdominal surgery. Lesions such as adenocarcinoma and benign adenomatous polyps are clearly outlined by the injected contrast medium; on account of abnormal vascularization some polypoid formations exhibit an individually increased blood supply. Even small polyps may be detected. The authors do not consider it possible at present to draw any conclusions as regards the histologic composition of the lesions. Operative intestinal arteriography allows the evaluation of the collateral blood supply of large segments of intestine.

ZUSAMMENFASSUNG

Die Verfasser beschreiben eine sichere und technisch einfache Methode, die bei der Bauchchirurgie benützt wird. Läsionen wie z. B. Adenokarzinome oder gutartige adenomatöse Polypen werden mit Hilfe des injizierten Kontrastmittels deutlich abgegrenzt. Auf Grund der abnormen Vaskularisation zeigen einige polypöse Bildungen eine individuell gesteigerte Blutzufuhr. Auch kleine Polypen können entdeckt werden. Die Verfasser sind der Ansicht, dass es im Augenblick noch nicht möglich ist, irgendwelche Schlussfolgerungen bezüglich des histologischen Aufbaues der Läsion zu ziehen. Die operative intestinale Angiographie ermöglicht die Deutung der kollateralen Blutversorgung grosser Abschnitte des Intestinums.

RÉSUMÉ

Les auteurs décrivent une méthode angiographique sans danger et techniquement simple, utilisée pendant les interventions chirurgicales abdominales. Des lésions telles que l'adénocarcinome et que les polypes adénomateux bénins sont nettement dessinées par le produit de contraste injecté; en raison d'une vascularisation anormale, certaines formations polypoïdes présentent une irrigation sanguine propre augmentée. Cette méthode permet de déceler même de petits polypes. Les auteurs ne pensent pas possible actuellement d'en tirer des conclusions sur la nature histologique des lésions. L'artériographie intestinale per-opératoire permet d'apprécier la vascularisation collatérale de grandes portions d'intestin.

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MEDIASTINAL HERNIATION AND DISPLACEMENT STUDIED BY TRANSVERSAL TOMOGRAPHY

by

H. Lodin

Mediastinal herniations and displacements have during recent years attracted increasing attention owing to the growing frequency of intrathoracic surgical procedures.

According to MAIER, mediastinal hernia has occurred when 'a portion of the mediastinal pleura of one side has penetrated through the mediastinum and invaginated a portion of the opposite pleural cavity'. It is to be distinguished from mediastinal displacement, in which the entire mediastinum is displaced, and which may exist in conjunction with herniation.

Certain 'weak spots', one in the anterior and two in the posterior mediastinum, have a direct bearing on the development of herniation (BÁRSONY and WALD; DOUB and JONES; MAIER; NITSCH). At these three points the mediastinal pleural reflexions are in close relation with one another (anterior and posterior mediastinal septa) and are separated, at the most, by loose connective tissue:

1. In the anterior mediastinum, at about the level of the first three or four costal cartilages, the 'area thymica'. This weak spot is limited ventrally by the sternum and dorsally by the great vessels.

2. In the postero-superior mediastinum, at the level of DV 3 to 5. This area is limited anteriorly by the oesophagus, trachea, and great vessels, and posteriorly by the vertebral column.

Submitted for publication 4 June 1957.

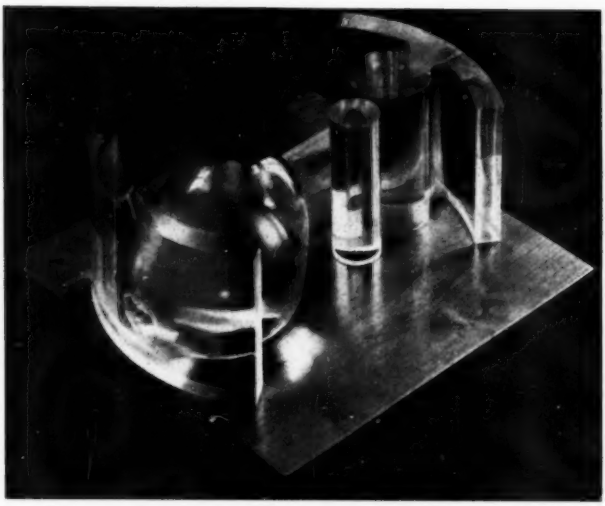


Fig. 1. Model thorax in plexiglass.

3. In the postero-inferior mediastinum, at the level of DV 5 to 11, and limited anteriorly by the heart and great vessels, and posteriorly by the aorta and vertebral column.

The postero-superior and postero-inferior weak spots are separated by the vena azygos (MAIER).

Any marked difference in pressure or volume between the two sides of the chest will predispose to herniation or displacement of the mediastinum. In experiments in cadavers, NITSCH was able to demonstrate the mechanism of the anterior type of mediastinal hernia. According to him herniation may take place only to the left in the postero-inferior mediastinum. The relations of the oesophagus and aorta are given as the reason, the oesophagus coming to overlap the aorta on any tendency to herniation from the left.

The roentgen diagnostics of these conditions have up to the present been based on fluoroscopy, conventional roentgenography, bronchography, ordinary tomography (SALINGER), and pneumo-mediastinum (SALMENKALLIO et coll.). Common to all these methods is the establishment of the presence of herniation or displacement, rather than a mapping out in details of the extent of the lesion. Mediastinal displacement can in general be diagnosed by these methods, whereas some herniae may escape detection or be incompletely revealed.

By means of *transversal tomography*, with tomograms taken at different levels, it is possible to assess the volume of the herniation and of

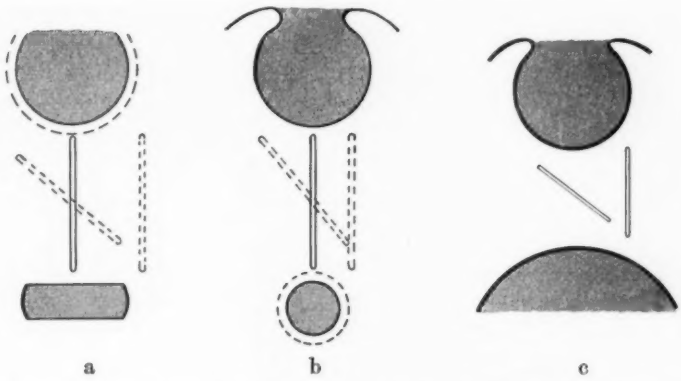


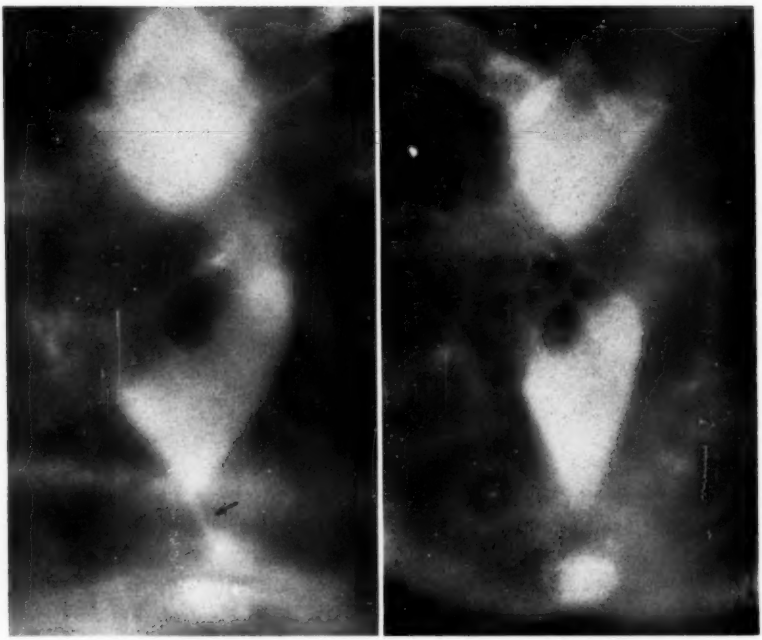
Fig. 2. Schematic drawings illustrating the requirements for the demonstration of: a) the 'anterior septum', b) the 'postero-superior septum', and c) the 'postero-inferior-septum'.

the expanding lung. To judge from the literature, the technique has previously been used for this purpose only by ROCHE et coll. (1953), who describe some cases of postero-superior and anterior herniation. No cases of postero-inferior herniation seem to have been studied by this method; and no investigation has been made into the application of transversal tomography in the diagnosis of the conditions in question. The very anatomy of the mediastinum and the limitations of the method itself limit the usefulness of the technique. It is therefore necessary to establish the relationship between the anatomy of the region and the principles of transversal tomography.

Anterior mediastinum. The anterior mediastinal septum is bounded anteriorly by the sternum, and posteriorly by the great vessels and the heart. The line of contact (anterior pleural line) between the two mediastinal pleural reflexions and the anterior wall of the thorax may show great variations, according to the standard textbooks of anatomy.

Posterior mediastinum. In its upper part the posterior mediastinal septum is limited posteriorly by the vertebral column, and anteriorly by the oesophagus, trachea, and great vessels. The sagittal depth is, as a rule, slight. In its lower part the septum is limited dorsally by the vertebral column and aorta and ventrally by the oesophagus and heart. The line of contact between the two pleural reflexions and the vertebral column (the posterior pleural line) has been investigated by DANELIUS, GLADNIKOFF, KNUTSSON, and others.

The depth of the anterior and posterior septum varies according to the shape of the thorax, the size of the heart and great vessels, and the degree of emphysema.



a b

Fig. 3. Transversal tomograms. a) Anterior mediastinal septum. b) Postero-superior mediastinal septum.

The anterior and posterior septa are both composed of narrow, linear or slightly curved structures of varying sagittal depth, and with relatively slight powers of absorption. They lie between structures (vertebral column, great vessels, heart and sternum), all of which have greater powers of absorption and greater volume, and which in turn show considerable variations in these respects. Whether under such circumstances a linear structure can be demonstrated depends upon its own volume and absorption properties, the amount of tangential (*i. e.* contour-forming) radiation, and the volume and absorption properties of the surrounding structures. Thus considerable differences are to be expected in the degree of representation of the 'septa' according to their position in the thorax.

In order to study the principles of reproduction of structures in the mediastinum I have had a model thorax made in plexiglass (Fig. 1). The parts are all removable, and the influence of the various elements can be examined separately. Thin sheets of plexiglass represent the septa, and the conditions in the anterior and posterior mediastinum can be reproduced schematically.

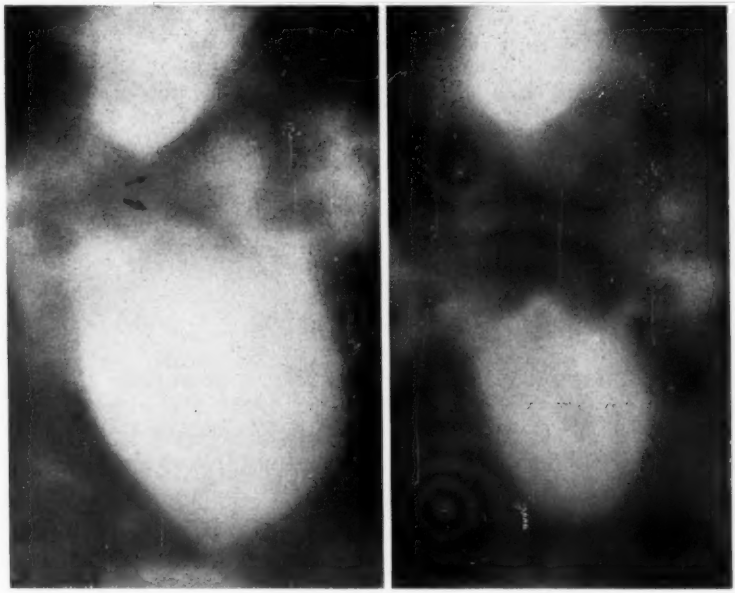


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Fig. 4. Transversal tomograms. a) Postero-inferior mediastinal septum. b) Usual appearance of the posterior mediastinum. Septum not discernible.

Experiments with the model thorax

These experiments were performed under the same technical conditions as a clinical examination. The apparatus was a Pantix Strator (ZUDER, Genoa), with a focus-object distance of about 250 cm, an object-film distance of about 50 cm, an angle of incidence of 25°, and no grid. Standard cassettes with ordinary double screens were employed, and the distance between layers was as a rule 2 to 3 cm. The septa were represented by a plane or slightly curved sheet of plexiglass 40 mm deep and 2 mm thick.

Anterior septum

If the great vessels are represented by a cylinder of plexiglass of up to 30 mm in diameter, and the sternum by a sheet of plexiglass measuring 10 × 30 mm, the anterior septum can be discerned no matter what angle it makes with the sternum or vessels. For demonstration of the septum when the diameter of the vessels is greater than 30 mm, the angle be-

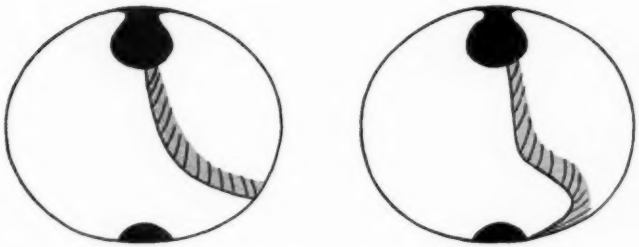

Fig. 5. Schematic drawings illustrating the distinction between displacement and hernia.

tween the septum and vessels must be such that radiation falling on the septum during rotation becomes primarily tangential (viz. not first passing through the sternum and great vessels) or that the entire septum lies on a level with or outside a sagittal plane passing through the outer contours of the vessels (Fig. 2 a, striped line)

Posterior septum

Superior mediastinum. If the upper thoracic vertebrae are represented by a plexiglass cylinder 30 mm in diameter, the diameter of the great vessels must not exceed 15 mm if the septum is to be shown, no matter what its position in relation to the vertebral column. (Fig. 2 b, full line). If this diameter is increased the same conditions will apply as for demonstration of the anterior septum (Fig. 2 b, striped line).

Inferior mediastinum. In the original model (Fig. 1), with vertebral bodies of about 50 mm in diameter and the heart of normal size, the posterior septum (even when 10 mm thick) can only be shown if the entire septum lies outside a sagittal plane through the outer contours of the vertebral body, or the radiation falling on the object during rotation becomes primarily tangential (viz. does not first have to pass through the heart or vertebral column). These conditions also apply when the adjacent lung shows massive consolidation (Fig. 2 c).

The experiments with the model thus show that, even when quite thick, the septum to be shown between large dense structures must lie on a level with or outside the outer contours of these structures, or must form an angle with them such that primarily active tangential radiation comes into play. The larger and less radiolucent the adjacent structures, the poorer will be the reproduetion.

In analogy to these experiments, good clinical demonstration of the anterior mediastinal septum and fairly good representation of a small

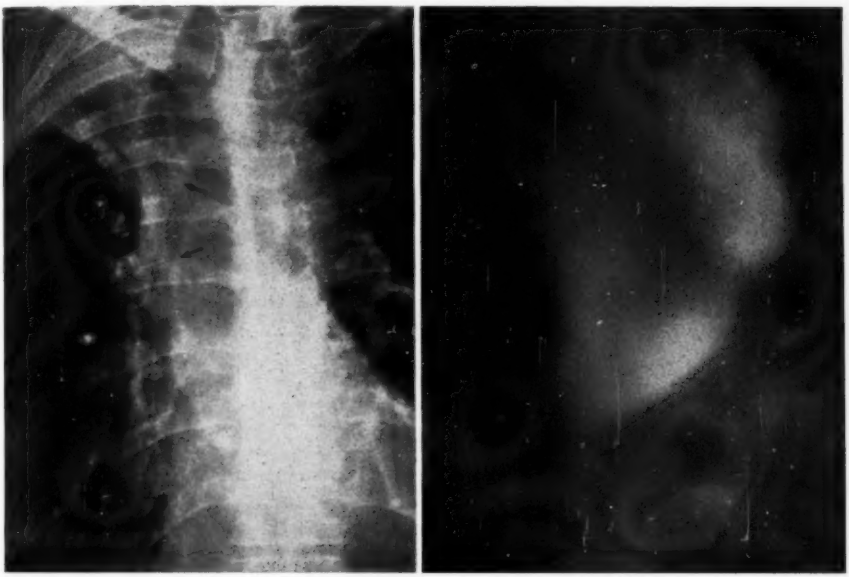

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Fig. 6. Case 1. a) Conventional roentgenogram. Collapsed right upper lobe. Upper part of mediastinum is pulled over to the right. Left lung expanded into the right side of the thorax (←). b) Transversal tomogram slightly above level of hilum shows considerable displacement of mediastinum to the right and moderate anterior herniation. Thickened anterior septum (←).

part of the superior part of the posterior septum (at any rate in children) may be anticipated, but poor reproduction of the inferior posterior septum no matter what state of the adjacent lung. Satisfactory reproduction of the posterior mediastinal septum is not to be expected except in cases of displacement at the level of or outside the outer contours of the thoracic vertebrae.

Transversal tomography in the clinical examination

The technical conditions were described in the first paragraph of the experiments with the model thorax. The highest tomogram was taken at the level of the sterno-clavicular joints, and the lowest at the level of the diaphragm.

Controls. These consisted of 20 subjects with no history of pulmonary disease, half of whom were aged 20 to 25, and half 11 to 12 years.

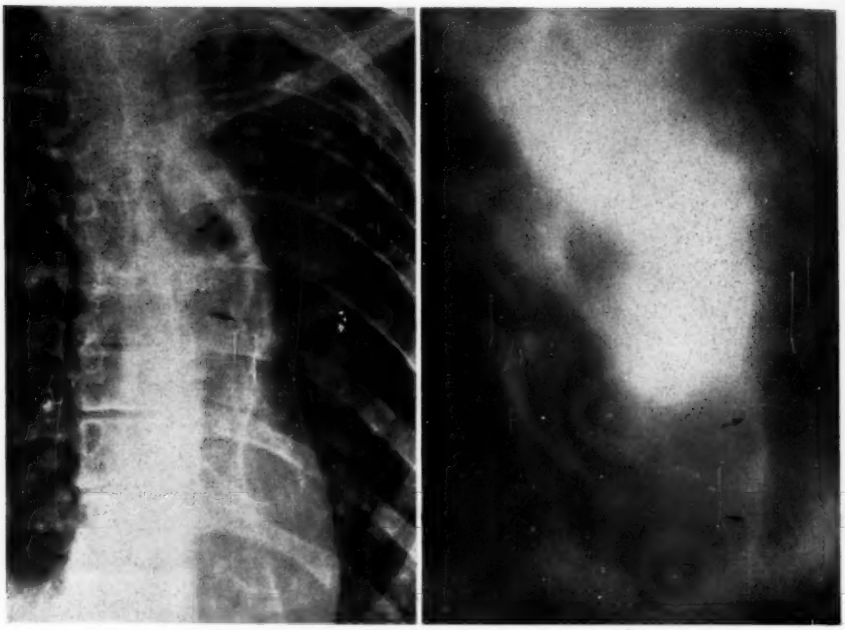

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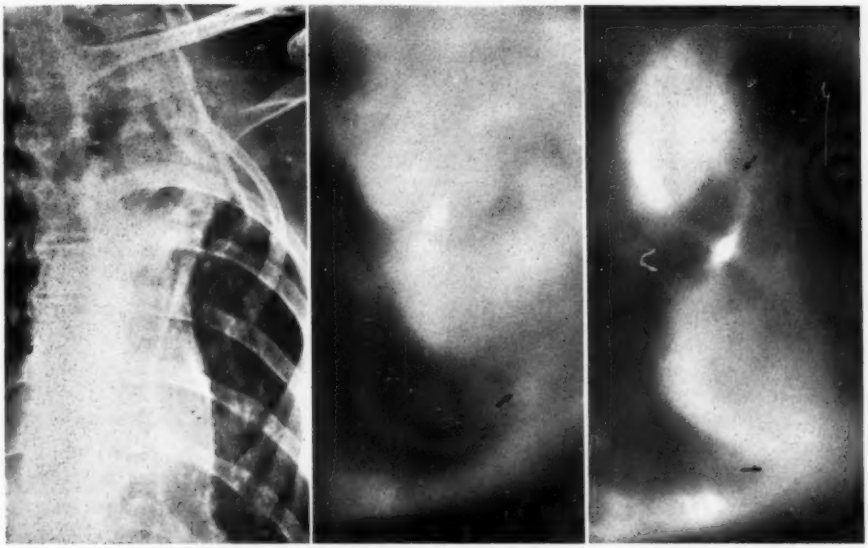
Fig. 7. Case 2. Preoperative examination. a) Conventional roentgenogram shows bilateral apical changes with displacement of mediastinum of the left and anterior herniation (→). b) Transversal tomogram confirms displacement to the left and anterior herniation (→).

Anterior septum. The septum was discernible in 19 of the 20 cases (Fig. 3 a). In 12 cases the pleural line was parallel with the sternum (in one case it lay to the right of the midline, in 5 cases in the middle, and in 6 cases to the left of the midline). In the remaining 7 cases the pleural line deviated (in one case the upper part lay to the right of and the lower part in the midline, and in the other 6 the upper part in the middle and the lower part to the left of the midline). In 18 cases the pleural line lay below the sternum, but in one case it lay 1 cm to the left of it. In 6 of these cases the septum formed an angle with the sagittal plane, and in 12 it was parallel with this. Finally, in 1 case the septum curved out beyond the border of the sternum. The septum varied in depth and length according to the shape of the thorax, the great vessels and the heart.

Posterior septum. The upper part was discernible in 9 of the 20 cases (Fig. 3 b), but its lower part could be seen only in 2 (Fig. 4 a). In 8 of the above 9 cases the septum lay in the midline, and in the ninth case to the left of the midline. The fact that the postero-superior septum could be



a b c

Fig. 8. Case 2. Examination 3 months after resection of left upper lobe. a) Conventional roentgenogram reveals displacement of the upper- and mid-mediastinum to the left. b) Transversal tomogram above level of hilum shows that the displacement has increased and that the anterior herniation has become more marked (→). c) Tomogram at level of hilum reveals a post-operative posterior displacement and herniation (←). At this level the anterior herniation is less marked (→).

seen in less than half the cases is thought to be partly due to the shallow nature, craniocaudally, of the region in question, and with an interval of 2 or 3 cm between the films some of the tomograms may have passed through the outer border of the region, or may have missed it altogether. In both cases in which the inferior part of the posterior septum was shown, it lay slightly to the left of the midline. In one of these cases the septum could be discerned in more than one tomogram.

Conclusions. The anterior septum can usually be demonstrated. As regards the posterior septum, its upper part is discernible in rather less than half of cases, and its greater, lower part only exceptionally. The conditions are similar among the older and younger groups of the control series.

Transversal tomography may therefore in normal cases be considered useful in the mapping out of the anterior mediastinal septum, but less so of the posterior septum, especially of its lower part. In examining the posterior septum, good frontal roentgenograms or frontal tomograms are required.

Fig. 9. Case 3. Conventional roentgenogram shows a left-sided empyema cavity with total destruction of left lung. Mediastinum pulled over to the left and there are signs of an anterior (→) and even a posterior (←) herniation.

Mediastinal herniation and displacement

On the basis of observations on transversal tomography, ROCHE et coll. define displacement and herniation as follows (Fig. 5).

Displacement. The mediastinal pleura of the expanding lung forms an acute angle with the anterior thoracic wall (direct contact between this part of the lung and the chest wall).

Herniation. The mediastinal pleura of the herniating lung makes an obtuse angle with the anterior wall of the thorax (no direct contact between this part of the lung and the chest wall).

The difference between the two states may also be expressed as follows. Displacement implies an abnormal situation of the line of contact between the anterior or posterior pleural reflexion and the anterior thoracic wall or the vertebral column. Herniation implies crossing of the plane connecting these two lines. The two conditions may be, and in fact often are, combined. It is of practical importance to distinguish between them. When displacement is present the surgeon may encounter pleura from

the opposite side, and thus accidentally induce pneumothorax on that side. This risk is not run in the case of pure herniation.

The degree of herniation or displacement is determined by the presence of adhesions between the mediastinal pleural reflexions and the vertebral column or anterior thoracic wall, and the direction of the traction exerted by the affected lung in relation to the mediastinum. Thus the tendency to displacement should be greater in left-sided than in right-sided lesions because of the shape and position of the heart. Continued rotation of the heart to the left and posteriorly would offer less resistance than rotation to the right and anteriorly.

It is usually possible to detect in the anterior mediastinum the line of contact between the pleural reflexion and the thoracic wall, and the distinction between anterior displacement and herniation can therefore be made. In the postero-inferior mediastinum this is notably difficult, and in most cases impossible, if the line of contact and the posterior septum remain within the outer contours of the vertebral column. Posterior herniation and displacement within these limits are thus inaccessible by transversal tomography. Displacement can never therefore be excluded, even in cases of apparently pure posterior herniation.

Illustrative cases

Case 1. A woman, aged 48 years, with a 9-year history of right-sided apical tuberculosis previously treated by pneumothorax. In the conventional roentgenogram (Fig. 6 a) the collapsed, right upper lobe is seen. The mediastinum, particularly the upper part, is pulled over to the right, and the left lung has expanded into the right side of the thorax. The transversal tomogram (Fig. 6 b) shows, slightly above the level of the hilum, considerable displacement of the mediastinum to the right, and moderate anterior herniation. The anterior septum is thickened.

Case 2. A woman, aged 33 years with a 14-year history of pulmonary tuberculosis, most marked in the left apical region. The conventional roentgenogram (Fig. 7 a) shows bilateral apical changes, with displacement of the mediastinum to the left and probable anterior herniation. The preoperative transversal tomogram (Fig. 7 b) confirms the moderate displacement to the left of the entire anterior mediastinum above the level of the hilum, and the anterior herniation. The anterior pleural line is displaced to the left, but the mediastinal pleural reflexions are slightly convex to the left.

After resection of the left upper lobe, conventional roentgenography 3 months later (Fig. 8 a) reveals increased displacement of the upper and middle mediastinum to the left. The mediastinal relations of the right lung are assessed with difficulty. Transversal tomography. The layer obtained above the level of the hilum (Fig. 8 b) shows that the traction on the upper mediastinum has increased (cf. Fig. 7 b), and that the anterior herniation has become more marked. In another section, at the level of the hilum (Fig. 8 c), the new, postoperative posterior displacement and herniation, and the now less marked anterior herniation are evident.

Case 3. A man, aged 22 years, with a 5-year history of bilateral tuberculosis treated by left-sided pneumothorax. Conventional roentgenography (Fig. 9) reveals a left-sided empyema cavity with total destruction of the left lung (basal bronchiectasis but no air-

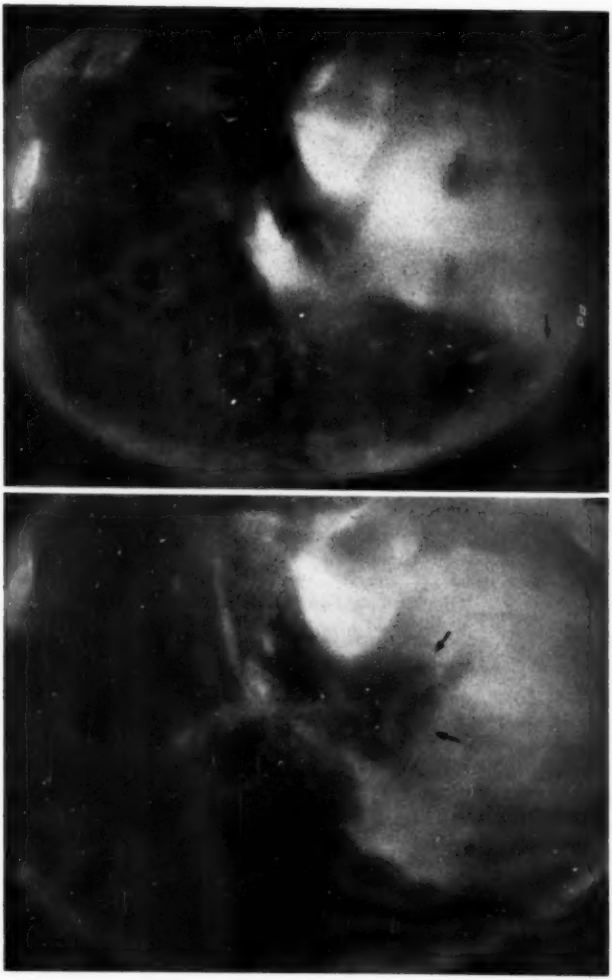


Fig. 10. Same case as in fig. 9. *Top:* Transversal tomogram at level of hilum shows marked displacement of mediastinum to the left with great anterior expansion of the right lung so that it has come in contact with the left flank. *Bottom:* Tomogram at level between hilum and diaphragm shows a large infero-posterior mediastinal herniation.

filled lung tissue). The mediastinum is pulled over to the left and there are signs of anterior herniation above the level of the hilum. Even in the posterior mediastinum, the right lung considerably overreaches the left-hand borders of the vertebral bodies. A transversal tomogram at the level of the hilum (Fig. 10, top) discloses marked displacement of the mediastinum to the left, with great anterior expansion of the right lung so that it has practically come in contact with the opposite chest wall out in the flank. In the tomogram at the level between the hilum and the diaphragm (Fig. 10, bottom) a large infero-posterior mediastinal herniation, which the vessels of the right lung can be seen to enter, is evident.

Discussion

The examples of mediastinal herniation and displacement presented serve to illustrate the improved means of diagnosis offered by transversal tomography. Cases of anterior herniation both to the right and to the left are described, but of the posterior type only herniation to the left is represented. ROCHE et coll. have described examples of postero-superior herniation to the right. Concerning the postero-inferior type, NITSCH has claimed that the anatomy of the region prevents herniation to the right. The findings on transversal tomography would suggest, however, that NITSCH's views may not be altogether correct. In Fig. 4 b the considerable space that exists between the oesophagus and aorta can be seen. It is hard to reason why the left lung should not here be able to herniate into the right side of the chest. NITSCH's conclusions were drawn from post-mortem material, in which, as in expiration, the oesophagus and aorta lie in close contact. In the living body the distance between these two structures may be considerable. I have not yet observed herniation in that direction, but I wish to stress, however, that postero-inferior herniation to the right is theoretically possible. To this problem I shall return when I have seen enough cases of rightsided lesions to be able to form a more definite opinion.

The increase in mediastinal displacement and herniation following lobectomy is evident from Case 2. Thoracic surgeons are not yet agreed concerning the extent to which resection should be combined with thoracoplasty with the object of stabilizing the mediastinum. Transversal tomography, better than any other diagnostic aid, provides a means of assessing the size of displacements and herniations. The use of this method for the pre- and post-operative examination of a large series of cases treated by thoracoplasty and pulmonary resection should help to clear up the doubt which exists, and to establish whether or not thoracoplasty is a desirable complement to the latter from this viewpoint.

SUMMARY

The principles of transversal tomography in the demonstration of the anterior and posterior mediastinal septa were established in experiments on plexiglass models and the conclusions confirmed in a series of normal subjects. Examples of different types of mediastinal displacement and herniation are given. The advantages of transversal tomography as an aid to the more exact measurement of the extent of such changes are stressed.

ZUSAMMENFASSUNG

Die Hauptprinzipe der transversalen Tomographie für die Sichtbarmachung der vorderen und hinteren Mediastinalsepta werden experimentell an Plexiglasmodellen festgestellt. Die Schlussfolgerungen werden an einer Reihe von Normalpersonen bekräftigt. Beispiele von verschiedenen Typen von Verschiebungen und Brüchen des Mediastinums werden gegeben. Die Vorteile der transversalen Tomographie als ein Hilfsmittel für genauere Messungen des Ausmasses derartiger Veränderungen werden hervorgehoben.

RÉSUMÉ

L'auteur a établi, par une expérimentation sur des modèles en plexiglass, les grands principes de l'application de la tomographie transversale à la démonstration des septums médiastinaux antérieur et postérieur. Ses conclusions ont été confirmées sur une série de sujets normaux. L'auteur donne des exemples de différents types de déplacements et de hernies du médiastin. Il souligne les avantages de la tomographie transversale pour contribuer à mesurer plus exactement l'étendue de ces modifications.

REFERENCES

Bársony, Th. und Wald, B.: Das Röntgenbild der oberen-hinteren schwachen Stelle des Mediastinums. Der prävertebrale, retroösophageale Lungenteil. Röntgenpraxis 8 (1936), 88.

Danelius, G.: Experimentelles über den Verlauf der oberen Lungengrenze im Röntgenbilde. Fortschr. Röntgenstr. 40 (1929), 249.

Doub, H. and Jones, H.: Hernia of the mediastinum. Amer. J. Roentgenol. 38 (1937), 297.

Gladnikoff, H.: A roentgenographic study of the mediastinum in health and in primary pulmonary carcinoma. Acta radiol. Suppl. 73 (1948).

Knutsson, F.: The mediastinal pleura. Acta radiol. 43 (1955), 265.

Maier, H.: Mediastinal hernia in the absence of pneumothorax. Amer. J. Roentgenol. 39 (1938), 687.

Nitsch, G.: Die »schwachen Stellen« des Mediastinums und ihre klinische Bedeutung bei pleuritischen Exsudat und Pneumothorax. Beitr. Klin. Tuberk. 18 (1910), 1.

Roche, G., Parent, J. et Mlle Renie, O.: Hernies du médiastin et tomographie transversale du thorax. J. franç. Méd. Chir. thorac. 7 (1953), 208.

Salinger, H.: The roentgen examination of the mediastinal lung hernia with reference to tomography. Acta radiol. 29 (1948), 130.

Salmenkallio, H., Tapiovaara, J. och Pätiälä, J.: Pneumomediastinografi i herniamediastinalis-diagnostiken. (Swedish.) Nord. Med. 53 (1955), 430.

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CALCIFICATION OF THE ASCENDING AORTA

by

Jack Lester and *C. E. Gudbjerg*

Calcification of the ascending aorta is relatively uncommon, even in advanced arteriosclerosis, excepting as a syphilitic condition, when the opposite is true. Vascular syphilis involves primarily the ascending aorta, the *Spirochaetes* being spread by the lymphatics which are particularly numerous just above the aortic valves. Calcifications at this site are believed to be secondary, syphilitic aortitis predisposing to localised arteriosclerosis (GORDON et coll.).

It was not until recently that the relationship between syphilis and calcification of the ascending aorta was recognized. In a discussion in 1942, SCHATZKI stated that the calcifications of the ascending aorta indicated syphilis, but the first study on the problem was not published until 1945 (JACKMAN & LUBERT) and from 1945 to 1956 six more papers appeared (LEIGHTON 1948, THORNER et coll. 1949, DE FAZIO & MARCICO 1951, WOLKIN 1954, and BRØBECK & IVE 1955). In series of from 24 to 122 cases of syphilitic aortitis, these authors had found calcification of the ascending aorta in between 18 % and 67 %. Later, MCCANN & PORTER (1956) and EPSTEIN (1957) have reported 19 and 20 cases, respectively, with calcifications in the ascending portion of the aorta.

Calcification of the ascending aorta in non-syphilitic patients is considerably more uncommon. JACKMAN & LUBERT found 2 in 62 cases of severe arteriosclerosis and THORNER et coll. 2 in 100 cases. Reviewing

Submitted for publication 6 June 1957.

400 chest films, unselected but corresponding in age and sex to his 39 cases of syphilitic aortitis, LEIGHTON found only 2 with calcifications. WOLKIN reported that only one out of his 54 cases of calcification in the ascending aorta was non-syphilitic. EPSTEIN, on the other hand, found 4 without syphilis in 20 patients with calcification of the ascending part of the aorta.

Unlike these previous authors, who have tackled the question in patients with syphilitic aortitis, we studied chest films representing a group of patients with neurosyphilis to estimate how often calcification of the ascending aorta may be expected in those with syphilitic infection of long duration.

Present series

The series comprises chest films of 200 neurosyphilitics (KOPP & RÅSCHOU-NIELSEN 1957) from the Dermatologic Department of the University Hospital (Director: Prof. H. HAXTHAUSEN). These were compared with 200 chest films of patients with arteriosclerosis of the aortic arch. The 400 roentgenograms were examined especially for calcification and ectasia of the aorta. If calcification of the ascending part was found in the arteriosclerotic group, the patient concerned was examined for syphilis.

The average age of the 200 neurosyphilitics (124 males and 76 females) was 52.4 years and that of the arteriosclerotic patients (82 males and 118 females) 65.0. Aneurysms of the ascending aorta were found in 4 and 2 patients respectively, but in analysing the material we paid no attention to this finding, since it is of no aetiological significance, calcifications being common in all kinds of aneurysms.

Among the 200 neurosyphilitics there were 21 (10.5 %) with definite calcification in the ascending aorta, whereas among the 200 arteriosclerotics there were only 3. Two of the latter, however, proved to be suffering from syphilis, so that among the 200 patients with calcification of the aortic arch only one without syphilis had calcification of the ascending part of the aorta. This patient, a 79-year-old woman, presented marked and uniform calcification of the entire thoracic aorta.

Ectasia of the aorta was found in 30 % of the 200 neurosyphilitics and in 64 % of the 21 patients with calcification of the ascending aorta. Among the 200 arteriosclerotics only 17.5 % had ectasia of the aorta. These findings indicate not only that a large proportion of the neurosyphilitics had syphilitic aortitis, but also that in about one-third o the patients with calcification of the ascending aorta, the calcification has preceded measurable ectasia. This accords with EPSTEIN's findings, *i. e.* 6 cases of aortic ectasia in 8 syphilitics with calcification of the

ascending aorta, whereas out of 8 cases of doubtful syphilis and 4 without syphilis he found ectasia of the aorta in 3 and 0, respectively. The only patient of the present series with calcification of the ascending aorta unaccompanied by syphilis had no ectasia.

Out of the 23 patients (21 neurosyphilitics plus 2 syphilitics from the arteriosclerotic group) with calcification in the ascending aorta 7 only had calcification at this site, whereas 11 also had calcification of the aortic arch and 5 calcification of the entire thoracic aorta. Thus, about one-third had isolated calcification of the ascending aorta. Furthermore, 3 patients had calcification of the aortic valves, so marked that it was demonstrable without tomography.

All the roentgenograms were routine ones of the chest in two projections, so that the 23 cases of calcification must be interpreted as a minimum figure. Six patients with doubtful calcifications were omitted. If the study had been carried out with the sole object of investigating calcification of the ascending aorta, and had included oblique views (particularly left oblique views), over-penetrated frontal views, and possibly tomography, the incidence of calcifications would no doubt have been higher.

Typical syphilitic calcification of the ascending aorta presents itself in the frontal view as a linear density of varying length, usually a few millimeters within the right border of the lower part of the ascending aorta. Faint calcifications are apt to escape detection, if they are not sought specially. With slight rotation of the patient from the frontal to the right oblique position, the calcification will disappear behind the spine. It may also be hidden by a dextroconvex dorsal scoliosis. On the other hand, a number of bony structures, such as the lateral sternal margin, the angles of the ribs, the tip of a transverse vertebral process, and the joint surfaces on both sides of the costo-vertebral joints, may be mistaken for faint calcification of the ascending aorta. In the presence of slight scoliosis, the right lateral surface of a dorsal vertebra may also give rise to such an error. Lastly, calcification of the right main bronchus and of the mediastinal pleura may resemble one of the ascending aorta. On further inspection, however, a mistake is easy to avoid, especially after reference to lateral or oblique views.

The demonstration of calcifications in the ascending aorta permits the recognition of syphilitic aortitis at a stage when the diagnosis may be difficult, the serologic reactions being not infrequently negative. Energetic antisyphilitic measures may then provide a chance of improving the poor prognosis in these cases.

SUMMARY

After a brief review of the literature, the authors survey a series of 200 patients with neurosyphilis and 200 with arteriosclerosis of the aortic arch. Calcification of the ascending aorta was found in 21 (10.5 %) of the former. Among the 200 patients with calcification of the aortic arch only one (0.5 %) without syphilis presented calcification of the ascending aorta.

ZUSAMMENFASSUNG

Nach einer kurzen Literaturübersicht unterziehen die Verfasser eine Serie von 200 Patienten mit Neurosyphilis und von 200 Patienten mit Arteriosklerose des Aortabogens einer kritischen Musterung. Verkalkung der Aorta ascendens wurde bei 21 Patienten (10.5 %) der ersten Gruppe gefunden. Von den 200 Patienten mit Verkalkung des Aortabogens zeigte nur ein Patient (0.5 %) ohne Syphilis Verkalkung der Aorta ascendens.

RÉSUMÉ

Après une brève revue de la littérature, les auteurs présentent une série de 200 malades atteints de neurosyphilis et une de 200 malades atteints d'artériosclérose de l'arc aortique. Ils ont trouvé une calcification de l'aorte ascendante chez 21 (10.5 %) malades de la première série. Parmi les 200 malades présentant une calcification de l'arc aortique, un seul indemne de syphilis (0.5 %) présentait une calcification de l'aorte ascendante.

REFERENCES

Brobeck, O. og Ive, T.: Betydningen af røntgenologisk påviselig aorta-ascendens-forkalkning for diagnosen aortitis luetica (Danish). Nord. Med. 54 (1955), 1495.

De Fazio, V. and Marcico, F.: quoted by Brobeck.

Epstein, B. E.: Calcification of the ascending aorta. Amer. J. Roentgenol. 77 (1957), 281.

Gordon, W. H., Parker Jr., F. and Weiss, S.: Gummatous aortitis. Arch. intern. Med. 70 (1942), 396.

Jackman, J. and Lubert, M.: The significance of calcification in the ascending aorta as observed roentgenologically. Amer. J. Roentgenol. 53 (1945), 432.

Leighton, R. S.: Calcification of the ascending aorta as a sign of syphilitic aortitis. Radiology 51 (1948), 257.

McCann, J. S. and Porter, D. C.: Calcification of the aorta as an aid to the diagnosis of syphilis. Brit. med. J. 1956: I, p. 826.

Râschou-Nielsen, W. and Kopp, H.: Cardiovascular syphilis in neurosyphilitic patients. To be published in: Acta dermat.venereol.

Schatzki, R.: Discussion of Cabot Case 28271. New Engl. J. Med. 227 (1942), 24.

Thorner, M. C., Carter, R. A. and Griffith, G. C.: Calcification as a diagnostic sign of syphilitic aortitis. Amer. Heart J. 38 (1949), 641.

Wolkin, A.: The significance of calcification in the ascending portion of the aortic arch. Radiology 62 (1954), 101.

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GROSS BILATERAL RENAL CORTICAL NECROSIS DURING LONG PERIODS OF OLIGURIA-ANURIA

Roentgenologic observations in two cases

by

Hans Moëll

Bilateral cortical necrosis occurs most frequently in association with concealed accidental hemorrhage (SHEEHAN and MOORE 1952). The main clinical sign is oliguria or/and anuria. A search of the literature failed to reveal more than one report of roentgenographic kidney changes in this condition (EFFERSØE et coll. 1954); in this case the diagnosis was made by needle-biopsy and calcifications were seen at tomography about two months after the onset of the disease. The patient survived and the pathologic changes ought to have been 'minor' or 'patchy' according to the four types of renal cortical necrosis described by SHEEHAN and MOORE. These authors made no roentgen examinations.

Gross bilateral cortical necrosis has formerly been of less interest to radiologists because it often runs a rapid and fatal course. By means of rational conservative therapy, and when indicated artificial kidney (dialysis, ultrafiltration), it has, however, become possible to keep cases of renal insufficiency alive for a long time. Thus, patients suffering

Submitted for publication 25 June 1957.

from acute reversible renal failure can now survive in spite of long-standing oliguria-anuria. This gave us an opportunity to follow the course of two cases of gross bilateral cortical necrosis which had been transferred to the Renal Clinic in Lund, where severe renal cases from all Sweden are treated. Cases of this type are since more than ten years examined with repeated roentgenographies of the kidneys. In cases of acute renal failure the kidneys are frequently enlarged during the initial stage and later become normalized, in a few cases smaller than normal.

If the outlines of the kidneys are obscured by fluid retention (retroperitoneal oedema, ascites), loss of fluid is as a matter of routine induced by diarrhoea and/or ultrafiltration of the blood in vivo. When the fluid retention has been overcome it is generally possible to register the kidney size. (ALWALL et coll. 1949, 1953, 1954.)

In the beginning, the clinical picture with oliguria-anuria and enlarged kidneys did not differ from that generally found in cases of acute tubular nephritis (tubular necrosis, lower nephron nephrosis, etc.). However, the irreversible renal insufficiency with long-standing oliguria-anuria (116 and 79 days, respectively) gradually rendered probable the clinical diagnosis of gross bilateral cortical necrosis. This was confirmed by the roentgenologic findings.

Case reports

Case 1. Primigravida, aged 27. When the patient was examined for a small hemorrhage about 5 months after the commencement of pregnancy, proteinuria was noted, and the blood pressure was 240/160 mm Hg. Vaginal caesarean section was later performed because of suspected separation of the placenta. During the operation the blood pressure dropped to a very low level and the loss of blood demanded repeated transfusions. The oliguria continued, the N. P. N. increased and oedema occurred. Six days after the operation the patient was transferred to the Renal Clinic, Lund.

Roentgen examination. Owing to retroperitoneal oedema and intestinal paralysis the kidneys could not be seen at the first examination. After reduction of the fluid retention the patient was re-examined. The kidneys were large (Right = 13.5 × 6.5 cm; Left = 13.5 × 6.5 cm) (Fig. 1). Fourteen days later the kidneys were just as large, but better defined. After a further 14 days the kidneys had decreased in size (Right = 12.5 × 6.0 cm; Left = 12.5 × 5.5 cm) and the outlines were irregular. On re-examination about 7 weeks after the operation a further decrease in size was noted and cortical calcifications had now appeared. The last roentgen examination one month later showed that the calcifications had increased in extent and the kidneys measured: Right = 10.0 × 4.5 cm; Left = 9.5 × 4.0 cm (Fig. 2).

Feeding difficulties made gastrostomy necessary. The operation was complicated by hemorrhage with decreasing blood pressure, followed by oliguria, *i. e.* added acute tubular nephritis. The patient's general condition thereafter deteriorated rapidly despite renewed dialysis and she died 116 days after the onset of the disease.

Histologic examination. Renal shrinkage (Weight of both kidneys = 95 g; Size: Right 8.0 × 3.5 cm; Left = 8.5 × 3.5 cm) with widespread bilateral cortical necrosis and traces of acute tubular nephritis.

Fig. 1. Case 1. Large kidneys.

Fig. 2. Same case as in fig. 1, about 15 weeks later. Considerable decrease in size of kidneys. Calcifications.

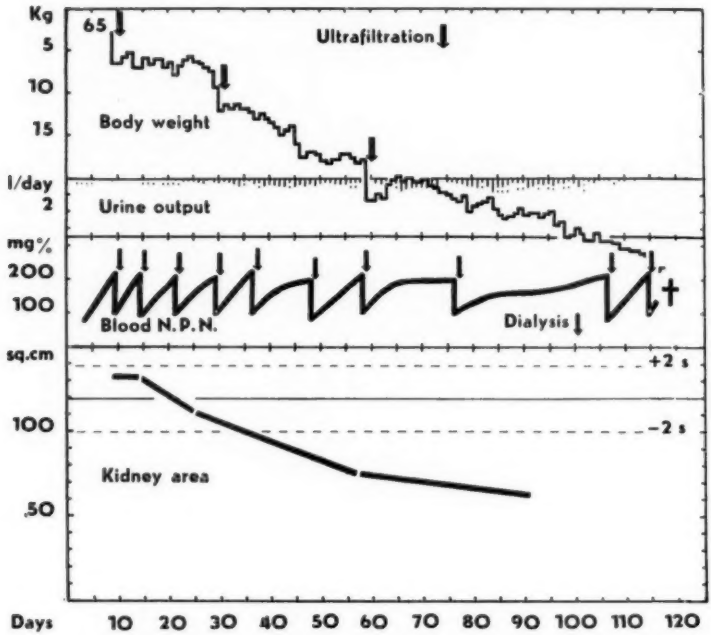

Diagram 1. Case 1. Illustration of the clinical course and successive decrease in the total area of the kidneys.

Case 2. Primigravida, aged 40. In the beginning the pregnancy was normal. Towards its termination the patient increased rapidly in weight and the blood pressure was 175/110 mm Hg. Heller's test was positive. In association with rupture of the membranes and poor uterine contractions the blood pressure rose to 250/130 mm Hg, and dropped to 110/80 mm Hg after bleeding from the vagina. Since the foetus was dead, delivery was concluded with perforation and extraction. This was followed by anuria, which persisted throughout the remainder of the patient's life (79 days). On the fourth day after the operation she was transferred to the Renal Clinic, Lund.

Roentgen examination. Enlargement of the kidneys: Right = Left = 14.0 × 6.5 cm. Three weeks later the kidneys had decreased in size (Right = 12.5 × 6.0 cm; Left = 12.5 × 5.0 cm) and during subsequent examinations a gradual decrease in the size of the kidneys was noted. They showed increased density without any demonstrable cortical calcifications. At the last control examination the kidneys were found to be: Right = Left = 10.0 × 4.0 cm.

Histologic examination. Renal shrinkage (Weight of both kidneys = 145 g. Size: Right = Left = 9.0 × 4.0 cm) with bilateral cortical necrosis.

The clinical course and the successive decrease in the total area of the kidneys are apparent from the Diagrams 1 and 2.

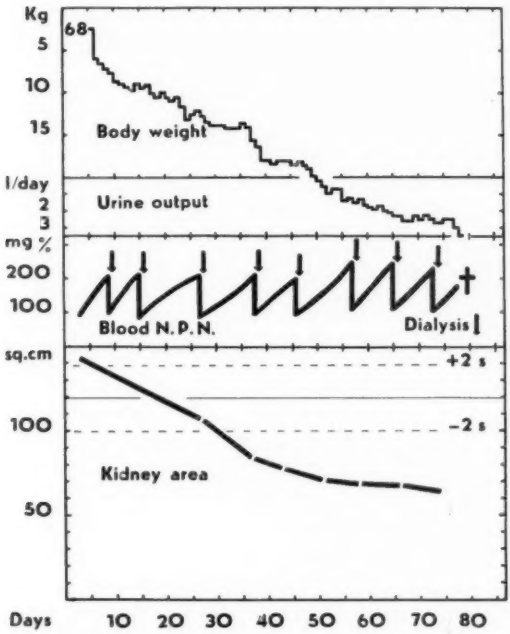

Diagram 2. Case 2. Illustration of the clinical course and successive decrease in the total area of the kidneys.

A reference value can be obtained by use of the usual mathematical term, $\sqrt{\text{area}}$. This permits assessment of any differences in the size of the kidneys from one examination to another. In Case 1, the volume of the kidneys measured in this way decreased from the first to the last examination to about 33 % and in Case 2 to about 30 %. In comparison with a normal female series in which the areas of the kidneys were determined (MOËLL 1956) the volume of the kidneys, as assessed in the same way, decreased to about 40 % of the original volume in both cases.

Discussion

The cases reported contracted acute renal failure in connection with delivery. The following roentgenologic observations were made.

In the early stage of the disease the size of the kidneys did not differ from that usually found in acute renal failure, *i. e.* it was distinctly increased.

In the course of 116 and 79 days, in the two cases respectively, a rapid shrinkage of the kidneys was, however, noted and the outlines became irregular.

Cortical calcifications appeared in Case 1 after about two months and the diagnosis was then beyond doubt. In the other case cortical calcifications also occurred, too small and delicate to be seen in the films obtained in vivo but discernible in post-mortem roentgenograms of the kidney specimen.

SUMMARY

Two cases of gross bilateral cortical necrosis with oliguria-anuria are described in which a rapid shrinkage of the kidneys was observed in repeated examinations, during a course of the disease of 116 and 79 days respectively. In one of the cases cortical calcifications were seen in ordinary roentgenograms.

ZUSAMMENFASSUNG

Zwei Fälle' von ausgedehnten kortikalen Nekrosen mit Oligurie-Anurie werden beschrieben, in welchen eine rapide Schrumpfung der Nieren bei wiederholten Untersuchungen während eines Krankheitsverlaufes von 116 und 79 Tagen beobachtet wurde. Bei einem dieser Fälle sah man kortikale Verkalkungen auf gewöhnlichen Röntgenbildern.

RÉSUMÉ

Présentation de deux cas de nécrose bilatérale massive de la corticale rénale avec oligurie-anurie; des examens répétés ont montré une rapide diminution de volume des reins au cours de l'évolution de cette affection en 116 et 79 jours respectivement. Dans un de ces cas, les radiographies simples montraient des calcifications corticales.

REFERENCES

ALWALL, N.: On the artificial kidney. VIII. Cases of acute renal failure with anuria-oliguria. Acta med. Scandinav. 1949, Suppl. 229, p. 3.

— and TORNBERG, A.: On the artificial kidney. XXIV. On the indications for dialytic treatment in acute renal failure ('lower nephron nephrosis' etc.) and the need for dialysis in rational renal therapy. Acta med. Scandinav. 147 (1953), 31.

— On renal failure complicating surgical diseases (laparotomy etc.) with special regard to conservative treatment, and the need for the artificial kidney (dialyser, ultrafilter) in rational renal therapy. (Acute tubular nephritis, chronic pyelonephritis and prostatic hypertrophy with urinary retention.) Acta chir. Scandinav. 108 (1954), 95.

EFFERSØE, P., GORMSEN, H., IVERSEN, P. og RAASCHOU, F.: Nyrebiopsy og dialyseproblemer (Danish). Ugeskr. f. Laeger 116 (1954), 1715.

MOËLL, H.: Size of normal kidneys. Acta radiol. 46 (1956), 640.

SHEEHAN, H. L. and MOORE, H. C.: Renal cortical necrosis and the kidney of concealed accidental haemorrhage. Blackwell Scientific publications, Oxford 1952.

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DISTURBANCES IN THE LUMBOSACRAL DYNAMICS FOLLOWING POLIOMYELITIS

by

J. Jirout, J. Šimon and *O. Šimonová*

During a study of the spinal dynamics in patients with nervous disease, roentgen examinations of the spine were carried out in a group of 60 subjects who had had poliomyelitis. As the neuromusculature is considered to be of the utmost importance in the maintenance of normal spinal mobility we expected that changes in its function following poliomyelitis might cause some deviations in the normal dynamics of the spine.

The material consisted of 60 young people, 38 boys and 22 girls, aged between 8 and 18 years, who had had poliomyelitis when they were 0 to 14 years old. The examinations were performed from 0 to 17 years after the acute stage of the disease. The form and degree of the lesions varied. Monoparesis and hypogenesis were present in the greater number of patients (21 cases). In 12, both lower extremities and the abdominal muscles were damaged. Monoparesis of a lower extremity with a lesion of the abdominal muscles were noted in 5 cases; in the same number of cases only the abdominal muscles were injured. Five patients showed quadriparesis; in 4 the quadriparesis was combined with paresis of the abdominal muscles. Two patients had monoparesis of an upper extremity. In 1 case unilateral lesions of an upper and lower extremity were discovered and in another there was paresis of both the upper and of one lower extremity. One patient

Submitted for publication 19 September 1956.

Fig. 1. 'Fixed lordosis' of the lumbar spine.

Fig. 2. 'Compensatory hypermobility' of the dynamical segments L5—S1 and L4—L5.

showed paresis of the lower and monoparesis of the upper extremities; in another one there was paraparesis of the upper extremities with a lesion of the abdominal muscles. In still another case, one upper extremity and the abdominal muscles were damaged; in 1 case only the m. gluteus medius was injured.

Lateral views of the lumbosacral spine in anteflexion, retroflexion, and erect, were included in all cases.

Of the total 60 cases the roentgenologic findings could be classified as 'marked disturbances of dynamics' in 52; in 8 only 'slight disturbances of dynamics' were found. In the group of 52 cases we noted the following abnormal roentgenologic signs:

1. A general decrease of motility of the lumbar spine up to complete 'fixed lordosis' (Fig. 1).
2. Fixation of two neighbouring vertebrae, the so-called 'dynamic block'.
3. Displacements between vertebrae.
4. Compensatory increased motility — 'compensatory hypermobility' (Fig. 2).

Out of these 52 cases we found fixed lordosis in 39, dynamic block in 17, displacements of vertebrae in 29, and compensatory hypermobility in 16. Some of these signs occurred in combination. In 16 cases fixed lordosis was associated with displacements of vertebrae. In 8 cases there was a combination of fixed lordosis with compensatory hypermobility and in 4 hypermobility occurred simultaneously with dynamic block. In all these cases the various types of lesions in the nervous system mentioned, with the exception of isolated lesions of the upper extremities, were present.

From an analysis of these findings the following conclusions may be drawn. Disturbances of the dynamics of the lumbosacral spine in patients with neuromuscular disorders are common and occurred in this material in 86.6 % of cases. Roentgenologic signs of disturbances of spinal mobility after poliomyelitis are not on the whole different from those we commonly find in alterations in the mutual relations of vertebrae due to degenerative changes in spondylosis deformans. Nevertheless, in contradistinction to the conditions encountered in spondylosis deformans we often found a decrease in the mobility of the whole lumbar spine in our patients. This was mostly manifested as a preservation of the lordotic form of the lumbar spine in anteflexion; for this sign we propose the term 'fixed lordosis'. In the group of 52 cases with marked dynamic deviations we found lordosis in 75 %. On the other hand in spondylosis deformans a dynamic block of two or three vertebrae was more frequent. Dynamic block occurred only in 32.7 % of the poliomyelitis cases apparently because of the high incidence of fixed lordosis. This was true also of compensatory hypermobility which occurred only in 30.7 % of the cases. Displacements of vertebrae were relatively frequent and were recorded in 55.7 % of cases; in 16 cases the displacements were present in combination with fixed lordosis to which they acted as a compensatory mechanism.

Of 39 cases with fixed lordosis, 36 had monoparesis or paraparesis of the lower extremities with or without a lesion of the abdominal muscles; in 3 cases only the abdominal or dorsal muscles were injured. It is therefore possible to consider fixed lordosis partly as a sign of a reactive contraction of the remaining spinal muscles, which results from increased stress especially in walking, and in poliomyelitics with muscular disorders of the lower extremities and/or the abdominal muscles. Moreover, the fibrosis of the injured spinal muscles is without doubt an important factor in the pathogenesis of the fixed lordosis. The frequency of fixed lordosis also explains the relatively high frequency of displacements of vertebrae and a low percentage of dynamic block and compensatory hypermobility.

No relation has been found on the one hand between the type of dynamic lesion and on the other hand the age of the patient when examined,

the age at the acute stage of the disease, and the interval between the latter and the examination.

The results of our investigation seem to indicate that disturbances of the spinal dynamics are very common following poliomyelitis and that the roentgenologic findings are very similar to those encountered in spondylosis deformans.

The question thus arises whether the appearances noted may be considered as signs of an increased disposition to the development of further disturbances of the spinal ligaments or of disc protrusion or prolapse, giving rise to symptoms of radicular or low back pain. Seemingly paradoxical conditions occur after poliomyelitis: it is generally agreed that radicular pain is rare following poliomyelitis although gross and often permanent lesions of the neuromuscular system may be in the foreground of the clinical picture and marked disturbances of the spinal dynamics are common. The difference between spondylosis deformans and poliomyelitis in this respect is determined by the condition of spinal muscles and ligaments. In spondylosis deformans with degenerated spinal ligaments a sudden very strong contraction of spinal muscles associated with a sudden involuntary unexpected movement or muscular stress is often the cause of disc prolapse or protrusion. This mechanism which acts only in persons with a good function of spinal muscles is out of question in poliomyelitics in whom the spinal muscles are incapable of such strong action. The weakness of spinal musculature and its fibrosis, resulting in so-called fixed lordosis, acts as protection against radicular discogenetic disorders in patients after poliomyelitis.

SUMMARY

The authors describe the results of a roentgenologic investigation of the lumbosacral dynamics in a material of 60 young people who had had poliomyelitis at various ages. It was established that disturbances of the lumbosacral dynamics in patients with neuromuscular disorders following the disease were common and occurred in nearly 87 % of cases. The 'fixed lordosis' sign is introduced and its significance in the differential diagnosis is discussed. The dynamic disturbances in poliomyelitics are compared with those in patients with spondylosis deformans. On the basis of this comparison an explanation of the fact that radicular pains are rare following poliomyelitis is sought for.

ZUSAMMENFASSUNG

Die Verfasser beschreiben das Ergebnis einer röntgenologischen Untersuchung der lumbosakralen Dynamik in einem Material von 60 jungen Menschen, welche in verschiedenem Lebensalter eine Poliomyelitis gehabt hatten. Es wurde festgestellt, dass Störungen der lumbosakralen Dynamik bei Patienten mit neuromuskulären Beschwerden

im Anschluss an die Erkrankung häufig vorkommen und in nahezu 87 % aller Fälle vorlagen. Das Symptom «fixierte Lordose» wird eingeführt und dessen Signifikanz in der Differentialdiagnostik wird besprochen. Die dynamischen Störungen bei Poliomyelitikern werden mit denen bei Patienten mit Spondylosis deformans verglichen. Auf Grund dieses Vergleiches wird eine Erklärung für die Tatsache gesucht, dass radikuläre Schmerzen nach einer Poliomyelitis selten sind.

RÉSUMÉ

Les auteurs présentent les résultats d'une étude radiologique de la dynamique lombo-sacrée sur une série de 60 jeunes gens qui ont été atteints de poliomyélite à des âges divers. Les auteurs ont établi que les perturbations de la dynamique lombo-sacrée sont fréquentes chez les malades présentant des séquelles neuro-musculaires de poliomyélite et se produisent dans près de 87 % des cas. Ils décrivent le signe de la «lordose fixée» et étudient sa valeur pour le diagnostic différentiel. Ils comparent les perturbations dynamiques des poliomyélitiques avec celles des malades atteints de spondylose déformante. Se basant sur cette comparaison, ils cherchent une explication à la rareté des douleurs radiculaires dans les séquelles de poliomyélite.

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RENAL DAMAGE IN RATS FROM THE LEAD SALT OF EDTA AND FROM UMBRADIL®

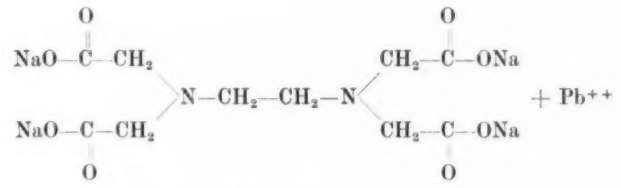
by

B. Ivemark and *S. I. Seldinger*

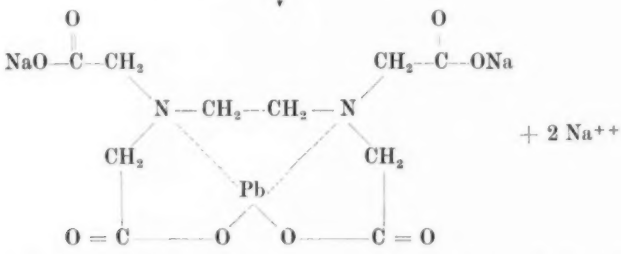
The use of high voltages in diagnostic roentgenology has caused increased interest in the use of elements of high atomic number as constituents of contrast media. The higher the voltage the more marked is the superiority of such an element as an absorber of roentgen rays. This is to some extent due to the fact that with increasing voltage more and more of the spectrum has a shorter wave-length than that of its K absorption limit; in this zone the roentgen absorption coefficient is larger than that of lighter elements, *e. g.* iodine.

It is well known that it is difficult to synthesize compounds of these metals of sufficiently low toxicity. It seemed possible that ethylene-diamine-tetra-acetic acid (EDTA or versene) might serve this purpose because of its ability to form unusually stable complex metal compounds. This stability is due to the simultaneous attachement by electron bond sharing of the metal with several atoms of the surrounding molecule:

Submitted for publication 14 July 1957.



Ethylene Diamine Tetra Acetic Acid Tetra Sodium Salt



Complexing Agent + Metal Ions ⟶ Metal Complex + Sodium Ions

Most metals, especially those which are polyvalent, can form these compounds, and the higher the pH of the solution, the more stable is the complex. A metal ion that has a greater ability than another to form a stable compound quantitatively displaces the latter from the molecule. The calcium EDTA is less stable than most metallic versenes and because of this has been found useful in cases of intoxication with lead and radioactive elements in hastening their excretion in the form of versenes (FOREMAN 1953; BAUER et coll. 1952; BESSMAN et coll. 1952; RUBIN et coll. 1953).

Because of its roentgen ray absorption power, the lead salt of EDTA was tried as a contrast medium by SAPEIKA (1954) in rats and rabbits. He reported that satisfactory urography was performed and that, with doses up to 0.1 g/kg bodyweight injected intravenously in rabbits, or 1 g/kg bodyweight injected subcutaneously or intraperitoneally in rats, there were "no ill effects". Later on, however, CLARK and TOMICH (1955) found that the excretion of large parenteral doses through the kidneys in rats was delayed over several days. In a recent paper, TJERNBERG (1957) reports retention of small amounts of lead in mice after three months, but no retention after eight months. This paper also contains calculations on the dissociation of lead EDTA in the body. CLARK and TOMICH also noticed that after the intravenous injection of 0.5 g/kg bodyweight there was evidence of slight renal damage (cloudy swelling of mid-zone and juxta-medullary tubules). Larger doses used in rabbits produced more advanced damage. No investigation of the effect of

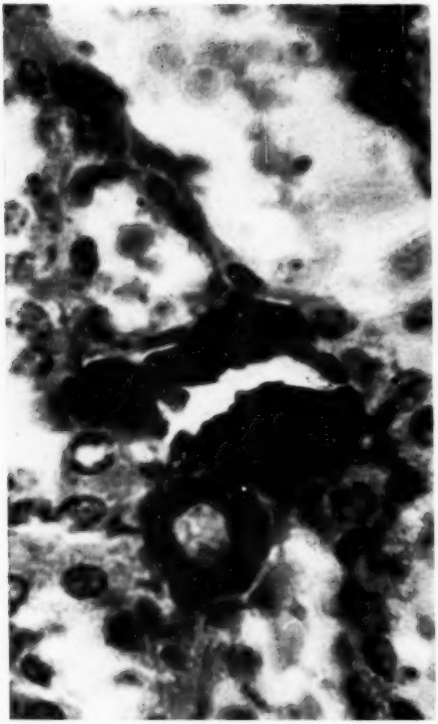


Fig. 1. Rat kidney 7 days after intravenous injection of 1.0 g/kg bodyweight lead EDTA. Deposits of mineral salt (apatite) in collecting tubules. Flattened and granular epithelium and desquamated epithelial cells of distal tubules. × 625.

Fig. 2. Rat kidney 7 days after intravenous injection of 2.0 g/kg bodyweight of Umbradil ®. Occasional hyaline cast in distal tubule. Normal epithelium in surrounding tubules. × 625.

intra-arterial injection of the compound on the kidneys has been reported.

It is known that the conventional iodine-containing contrast media have a certain toxic effect on the kidneys at least when large doses are administered intra-arterially (ALVALL et coll. 1955). We found it desirable to complete CLARK's and TOMICH's investigation with a comparison between such a contrast medium and lead EDTA, injected intravenously and intra-arterially.

Material

In a series of rats weighing 170—200 g, a 50 % aqueous solution of lead EDTA was injected intravenously and intra-arterially. For the intra-arterial injections 1 per cent calcium EDTA was added to this solution. A control series was injected with Umbradil 40 % (ASTRA), while in a few rats Ringer's solution was used, to which 7.2 % sodium chloride had been added. Thus the osmotic pressure of this solution, called hypertonic sodium chloride solution, was approximately the same as that of lead EDTA 50 %. The concentration of Umbradil chosen was such that its ability to prevent blackening of a film was definitely not inferior to that of the EDTA 50 %. The comparison was made by exposing the film at 150 kVp, after the roentgen beam had passed varying concentrations of Umbradil in increasing steps of 5 per cent together with the lead EDTA. The solutions were placed in compartments in the middle of an 18 cm thick plexiglass-water phantom. The smallest dose of the compounds injected was of the same order relative to the bodyweight as the largest dose of iodine-containing medium used in man.

The material was grouped as follows:

Intravenous injection. In 17 rats a caudal vein was injected without anaesthesia with 1.0 to 3.0 g/kg bodyweight lead EDTA. The rats showed no obvious signs of reaction. Three were killed after 7 days, 5 after 2½ months and the remainder after 6 months.

Seven rats were injected in the same way with 1.0 to 2.4 g/kg bodyweight Umbradil; 2 were killed after 7 days and 5 after 2½ months.

Three rats were injected with 1.0 to 2.0 g/kg bodyweight hypertonic sodium chloride solution and were killed after 2½ months.

Intra-arterial injection. In 7 rats the left common carotid artery was exposed under nembutal sodium anaesthesia, a needle or polyethylene catheter was inserted in the direction towards the aorta, and a ligature was placed around the artery. Then, 0.3 to 4.0 g/kg bodyweight lead EDTA with 1 per cent calcium EDTA was injected. The needle or catheter was removed and the vessel ligated.

One of these rats died within 15 hours and another within 45 hours. The remainder were killed after 15 to 21 hours.

Three rats were injected in the same manner with 0.4 to 0.8 g/kg bodyweight Umbradil and one with hypertonic salt solution. These were killed after 15 to 22 hours.

Chloroform was used in all cases to bring about death. The kidneys were removed 5 to 15 minutes after death; they were fixed in 10 per cent neutral formalin and embedded in the usual way. The sections were stained with haematoxylin-eosin and examined histologically.

Table 1

Occurrence of renal changes after intravenous injection of lead EDTA 50 %

	Dose	Glomeruli	Convoluted tubules	Collecting tubules
Animals killed after 7 days	1.0 g/kg bodyweight	—	++	+
	2.25 » »	—	++	—
	3.0 » »	—	++	++
Animals killed after 2½ months.....	1.25 » »	—	—	—
	1.25 » »	—	—	+
	2.0 » »	—	++	+
	2.25 » »	—	++	+
	3.0 » »	—	++	+

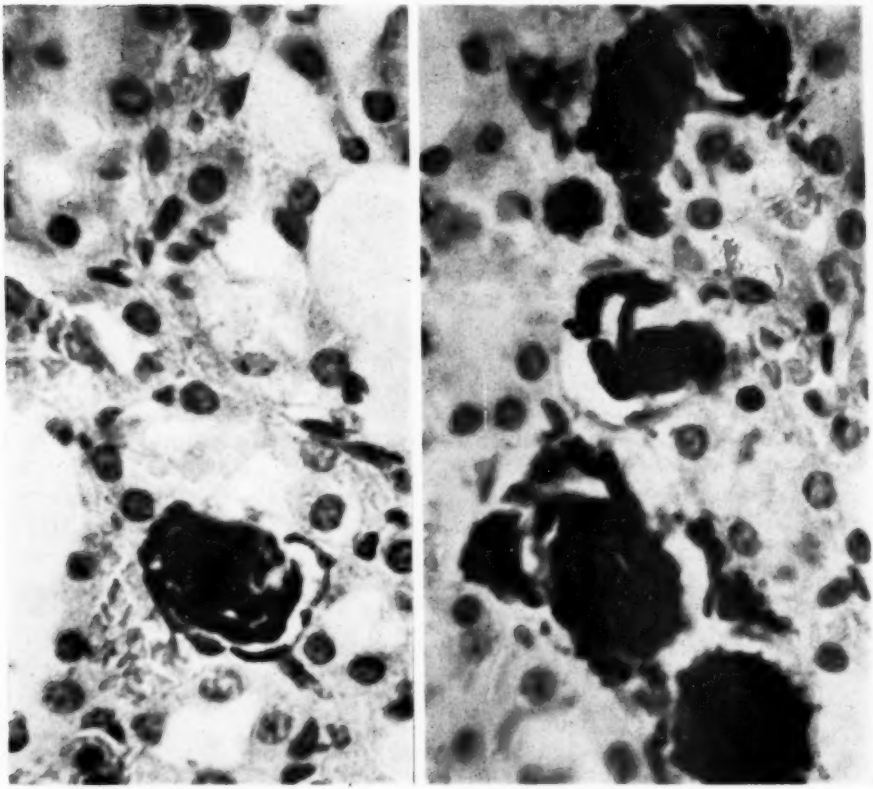


Fig. 3. Rat kidney 19 hours after intravenous injection of 1.4 ml hypertonic sodium chloride solution. Two fields from the same kidney showing mineral salt deposits in tubular lumen. × 625.

Table 2

Occurrence of renal changes after intravenous injection of Umbradil ® 40 % or hypertonic salt solution

	Dose	Glomeruli	Convoluted tubules	Collecting tubules
Animals killed 7 days after injection of Umbradil ...	1.2 g/kg bodyweight	—	+	—
	2.0 » »	—	+	—
Animals killed 2½ months after injection of Umbradil	1.0 » »	—	—	+
	1.2 » »	—	+	+
	1.8 » »	—	+	+
	2.0 » »	—	+	+
	2.4 » »	—	+	+
Animals killed 2½ months after injection of hypertonic sodium chloride solution	1.0 ml	—	—	++
	1.4 »	—	—	++
	2.0 »	—	—	++

Table 3

Occurrence of renal changes after intra-arterial injection of lead EDTA 50 %

Time of survival	Dose	Interstitial tissue	Periglomerular spaces	Convoluted tubules	Collecting tubules
21 hrs	0.3 g/kg bodyweight...	++	+	++	—
15 hrs	0.75 » » ...	++	+	++	—
15 hrs	1.0 » » ...	++	+	++	—
15 hrs[1]	1.25 » » ...	++	+	++	—
21 hrs	2.0 » » ...	++	+	+++	
45 hrs[1]	2.5 » » ...	Post-mortem autolysis			
15 hrs	4.0 » » ...	++	+	+++	—

[1] died spontaneously.

Histologic changes in the kidneys

Intravenous injections. Injections of lead EDTA were associated with tubular changes (Table 1). The lesions encountered in the rats killed at 6 months were indistinguishable from those seen in the rats killed at 2½ months and at 7 days. Many proximal and distal convoluted tubules as well as limbs of the loop of Henle contained hyaline proteinous casts. The epithelial lining of these parts of the nephrons showed granular, flattened cytoplasm and frequently desquamated cells. The straight collecting tubules, and the papillary ducts contained deposits of mineral salts in varying amounts (Fig. 1). The deposits were examined by roentgen-ray diffraction (CARLSTRÖM 1955) and were shown to contain basic calcium phosphate (apatite).

Table 4

Occurrence of renal changes after intra-arterial injection of Umbradil® 40 % or hypertonic sodium chloride solution

Time of survival	Dose	Interstitial tissue	Periglomerular spaces	Convoluted tubules	Collecting tubules
15 hrs	0.4 g/kg bodyweight Umbradil	+	—	+	—
20 hrs	0.6 » » »	+	—	—	+
22 hrs	0.8 » » »	+	—	—	+
19 hrs	0.5 ml hypertonic sodium chloride solution	+	—	—	—

After injections of Umbradil® similar changes appeared, but they were not so prominent (Table 2). Here and there, tubules contained proteinous casts (Fig. 2) and desquamated epithelial cells, but in general the epithelium was intact. Very occasionally, straight collecting tubules showed deposits of mineral salts of the same type as found after lead EDTA injections.

After injection of hypertonic sodium chloride solution, apatite deposits more prominent than those seen following injection with lead EDTA, were present in the straight collecting tubules and the papillary ducts (Table 2, Fig. 3). Otherwise, the kidneys were normal histologically.

Intra-arterial injections. After the administration of lead EDTA (Table 3) there were prominent areas of haemorrhage in the interstitial tissue (Fig. 4) at the level of the cortico-medullary junction and occasional haemorrhages into the periglomerular spaces. The periglomerular haemorrhages were not limited to the juxta-medullary zone of the cortex. A few tubules contained hyaline proteinous casts and the epithelial cells of the proximal convoluted tubules showed granular change with occasional desquamated cells in their lumina. There were no deposits of mineral salts. The changes found after 15 hours were indistinguishable from those seen after 21 hours.

There were a few areas of haemorrhage in the interstitial tissue after injections of Umbradil® or hypertonic sodium chloride solution (Table 4). No haemorrhage was present in the periglomerular space. The tubules showed hyaline proteinous casts in one case but no epithelial changes (Fig. 5), while two other cases presented very occasional small deposits of apatite in the collecting tubules.

Discussion

Our results show that the renal damage after intravenous and intra-arterial injection of large dóses of lead EDTA 50 % is more extensive than when comparable doses Umbradil® 40 % is employed. After intravenous

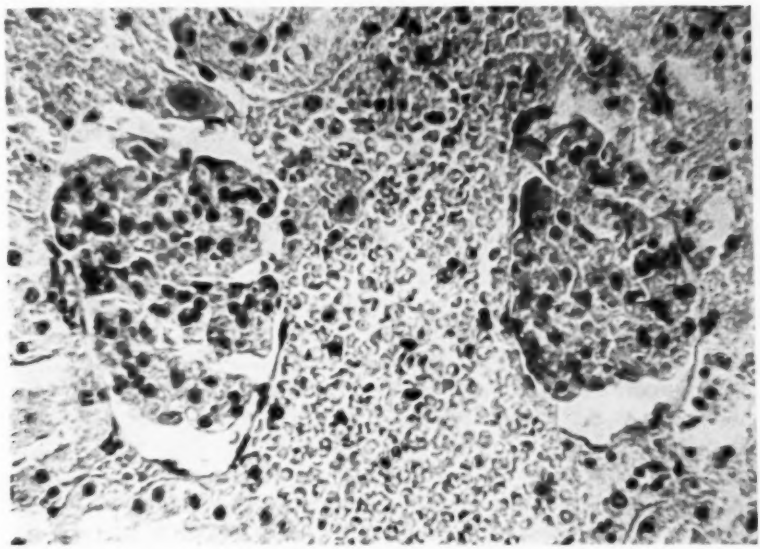


Fig. 4. Rat kidney 21 hours after intra-arterial injection of 0.3 g/kg bodyweight EDTA. Interstitial haemorrhage between two glomeruli. × 190.

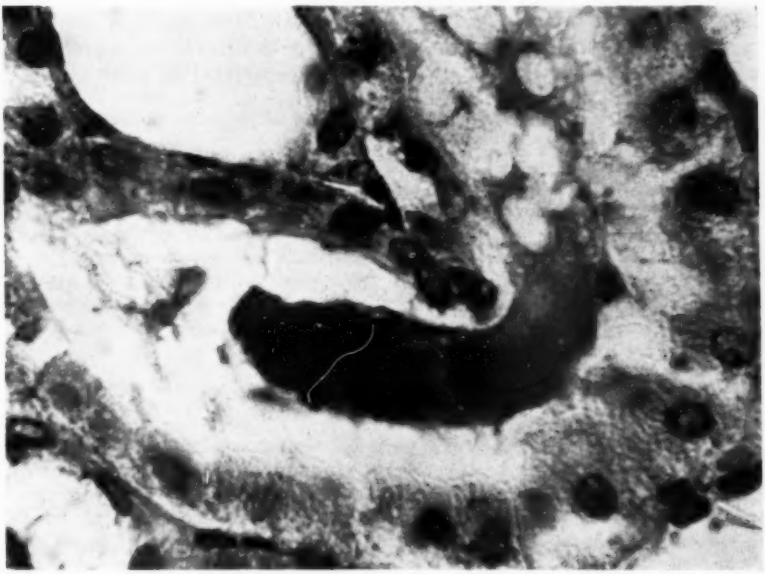


Fig. 5. Rat kidney 20 hours after intra-arterial injection of 0.6 g/kg bodyweight of Umbradil ®. An occasional hyaline cast in proximal tubule. Normal epithelium. × 625.

injection tubular damage with epithelial changes, casts and deposition of mineral salts followed the use of both contrast media. Following intra-arterial injections haemorrhages were noted in addition to a granular change of the tubules with collection of casts. The difference between the renal damage caused by the two contrast media was greater after intra-arterial use than after intravenous injection. This may, however, depend upon the difference in survival time (15 to 21 hours and 7 to 45 days, respectively). After injection of hypertonic sodium chloride, disseminated apatite deposits appeared, without any other changes. In the present material no conclusion can be drawn concerning this finding.

The histological renal changes following intravascular injection of lead EDTA described in this paper are not in any way specific. They also occur to a lesser extent after injection of Umbradil. Furthermore, morphologic alterations of the kidneys of somewhat similar type have been demonstrated in the rabbit after renal ischaemia (FAJERS 1955). From this morphological similarity no conclusions can be drawn concerning the pathogenesis. The possibility that the renal changes in our material represent the result of anoxia rather than toxic action by the contrast medium itself must be considered.

The results obtained should not preclude continued study of EDTA compounds for their employment as radiographic contrast media. It is possible that there are other complexes which are more suitable as regards toxicity and absorption power. On the other hand it may be that the deleterious effect upon the kidneys is due to the EDTA complex as such. Thus it might be desirable to test the calcium EDTA, used in therapy, from this point of view.

SUMMARY

The histological renal changes in rats following intravenous and intra-arterial injections of lead EDTA are briefly described. After intravenous injections, tubular epithelial degeneration with the formation of hyaline casts and mineral deposits were found. Following intra-arterial injection of EDTA, interstitial and periglomerular haemorrhage occurred in addition to moderate epithelial changes of the tubules. The lesions were similar to, but more severe than those appearing after the injection of comparable doses of Umbradil ®.

ZUSAMMENFASSUNG

Die histologischen Nierenveränderungen bei Ratten nach intravenöser und intraarterieller Injektion von Blei EDTA werden kurz beschrieben. Nach intravenöser Injektion wurde tubuläre-epitheliale Degeneration mit der Formation von hyalinen Zylindern und Mineralablagerungen gefunden. Nach intraarterieller Injektion von EDTA kamen ausserdem interstitielle und periglomeruläre Blutungen neben mässigen epithelialen Veränderungen der Tubuli vor. Die Veränderungen waren ähnlich aber schwerer als die, welche nach vergleichbaren Dosen von Umbradil ® auftreten.

RÉSUMÉ

Les auteurs décrivent brièvement les modifications histologiques rénales chez des rats à la suite d'injections intraveineuses et intra-artérielles de sel de plomb de l'EDTA. Ils ont observé après injection intraveineuse une dégénérescence de l'épithélium tubulaire avec formation de cylindres hyalins et dépôts minéraux. Après injection intra-artérielle d'EDTA, des hémorragies interstitielles et périglomérulaires sont apparues, en plus de lésions tubulaires modérées. Ces lésions sont similaires mais plus graves que celles qui apparaissent après injection de doses comparables d'Umbradil ®.

REFERENCES

Alvall, N., Johnsson, S., Tornberg, A. and Werkö, L.: Acute renal failure following angiography, especially the risk of repeated examination, revealed by eight cases (two deaths). Acta chir. scandinav. 109 (1955), 111.

Bauer, R. O., Rullo, F. R., Spooner, Ch. and Woodman, E.: Acute and subacute toxicity of ethylene diamine tetraacetic acid (EDTA) salts. Fed. Proc. 11 (1952), 321.

Bessman, S. P., Reid, H. and Rubin, M.: Treatment of lead encephalopathy with calcium versenate. Med. Ann. Distr. Columbia 21 (1952), 312.

Carlström, D.: X-ray crystallographic studies on apatites and calcified structures. Acta radiol. Suppl. 121 (1955).

Clark, B. J. and Tomich, E. G.: Pharmacological studies on lead E. D. T. A. British Med. J. (1955), p. 831.

Fajers, C. M.: On the effect of brief unilateral renal ischemia. Acta path. microbiol. scand. Suppl. 106 (1955).

Foreman, H.: The use of chelating agents for accelerating excretion of radio-elements. J. Amer. Pharm. Ass. (Scient. ed.) 42 (1953), 629.

Rubin, M.: Chelation, key to metal ion control. Drug and Cosmetic Ind. 74 (1954), 496.

— Gignac, S., Bessman, S. P. and Belknay, E. L.: Enhancement of lead excretion in humans by disodium calcium ethylene diamine tetraacetate. Science 117 (1953), 659.

Sapeika, N.: Lead EDTA complex. A watersoluble contrast medium. Sth. Afr. med. J. 28 (1954), 759.

Tjernberg, B.: Roentgenographic and toxicologic studies on lead EDTA. Acta radiol. 47 (1957), 308.

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AN IMAGE TRANSFORMING SCANNING PHOTOMETER FOR DISPLAYING SMALL DENSITY GRADIENTS

by

Bertil Jacobson

A photographic film can contain small density gradients invisible to the naked eye. The human eye can detect light intensity differences no smaller than about 0.5 per cent even when the brightness level is optimal. This corresponds to a density difference of about 0.002 units. Under suitable conditions, smaller differences may represent information that cannot be observed directly. The present instrument was developed in order to display and determine quantitatively such small density gradients. The method might find applications in medical and industrial radiography for observing weak contrasts, and in film spectroscopy for recording weak or overlapping lines, and in certain other fields of photography.

Principle of operation. The gradient of the film density in a surface element ds can be written

$$dD/ds = (-\log e)(1/T)(dT/ds) \qquad (1)$$

where $\log e$ is a constant, $D = \log (1/T)$ the film density, and T the transmission.

The factor dT/ds, which represents the change of transmission within the surface element (or image element), can be determined ex-

Submitted for publication 20 May 1957. Paper presented at the 4th Intern. Instr. Measurements Confer. in Stockholm, 17—19 September, 1956. The research reported was supported by Knut och Alice Wallenbergs Stiftelse.

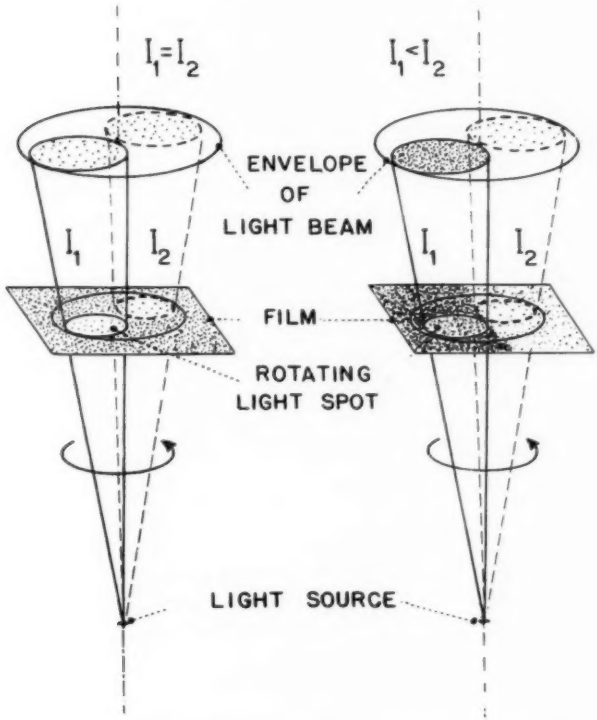

Fig. 1. The absolute value of the density gradient obtained from the intensity variations from a rotating spot of light.

perimentally by measuring the transmitted intensity of a rotating light spot as indicated in Fig. 1. If the film density is constant within the surface area scanned by the rotating light spot, the transmitted light is constant. But if a gradient exists, the transmitted light intensity varies with a frequency given by the speed of rotation of the light spot. When the transmitted light is measured by a photomultiplier the a. c. component of the multiplier current becomes proportional to dT/ds. Because of the circular motion of the spot this will be true for a gradient in any direction, which would not be the case with a simple scan followed by a differentiating circuit. By multiplying the current with a factor $1/T$, an a. c. current proportional to the absolute value of the density gradient is obtained. The multiplication is accomplished through a feedback system described below.

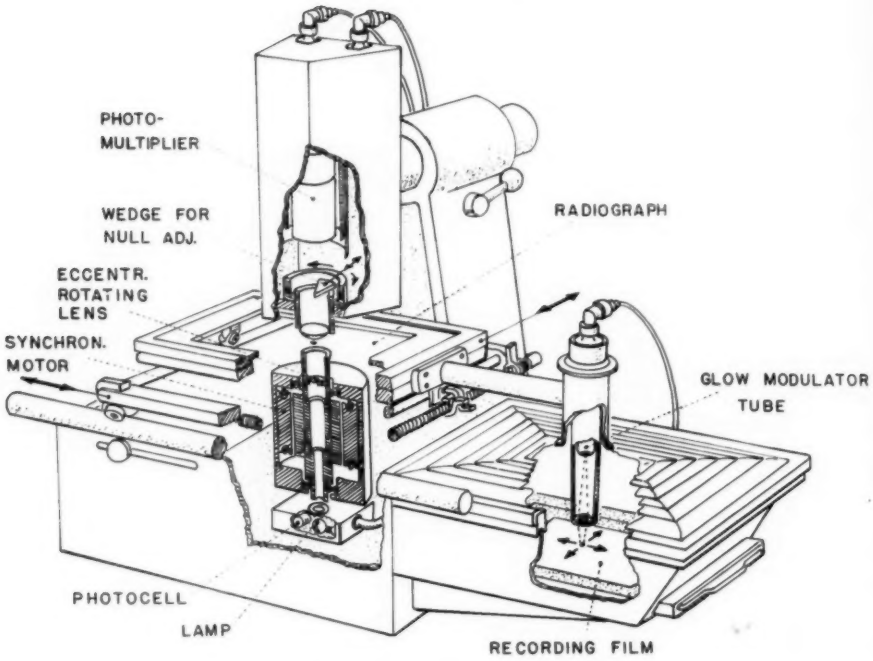

Fig. 2. The scanning system.

Mechanical and optical design. The spot of light from an incandescent lamp is focussed by a lens on the radiograph to be transformed. The lens is placed eccentrically inside the hollow axis of a synchronic electric motor running at 25 r. p. s. The eccentricity causes the light spot to scan the radiograph in the desired circular path. The diameter and the eccentricity of the light spot can be varied between 0.05 and 0.3 cm. The transmitted light is collected on the photocathode of a 6291 DuMont photomultiplier tube by a second lens. The position of this lens and the photomultiplier is such that the light hits exactly the same part of the photocathode throughout the rotation. Through this, errors are eliminated due to varying sensitivity of different parts of the photocathode.

In order to compensate for mechanical and optical defects causing spurious light variations, a compensating wedge is placed between the light collecting lens and the multiplier. The angular position and the radial depth of the wedge is adjusted for zero a. c. output from the multiplier when no gradient is present in the radiograph.

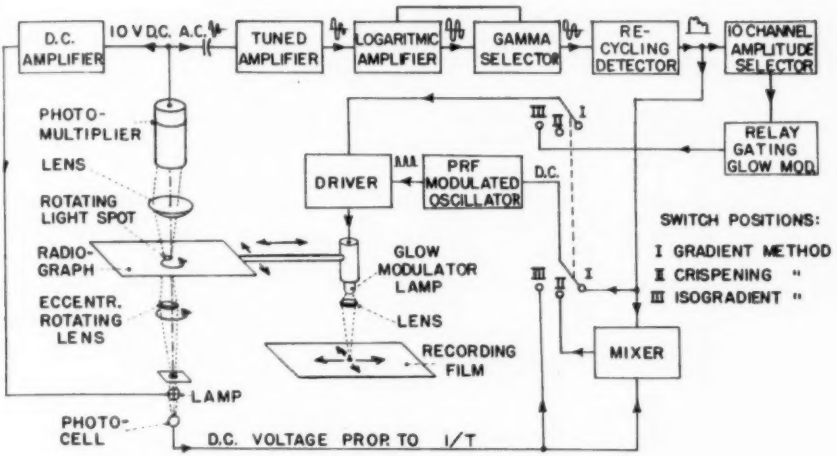

Fig. 3. Block diagram of the electronic circuits.

The radiograph moves in two perpendicular directions through an electromechanical device in such a way that the radiograph is scanned by the rotating light spot in parallel lines. The speed of this rectilinear scan, 0.3 to 0.1 cm per second, is slow compared to the peripheral speed of rotation of the light spot. A glow modulator tube is coupled to the scanning movement. The position of the light spot from this tube, focussed on the recording film, corresponds to the position of the rotating light spot on the radiograph. The geometric dimensions of the original image and the recorded image thus becomes identical. The glow modulator tube is fed with a current that depends on the density gradient of the original image in one of three different ways, as will be described below.

The system described for producing the rotating light spot has certain advantages over some other methods tested. The method is very stable and allows extreme sensitivity in the determinations of the gradient. The rotational speed of 25 c/s is, however, comparatively slow, but could be increased through the insertion of certain optical prisms (Dove prisms). The mechanical system used has been found to be superior to flying spot tube devices for producing the rotating spot; complicated stabilizing circuits must be employed to obtain constant light output from such tubes.

Electronic design. The block diagram in Fig. 3 shows the associated electronic units. The light intensity of the lamp scanning the radiograph is made to be inversely proportional to the average film transmission

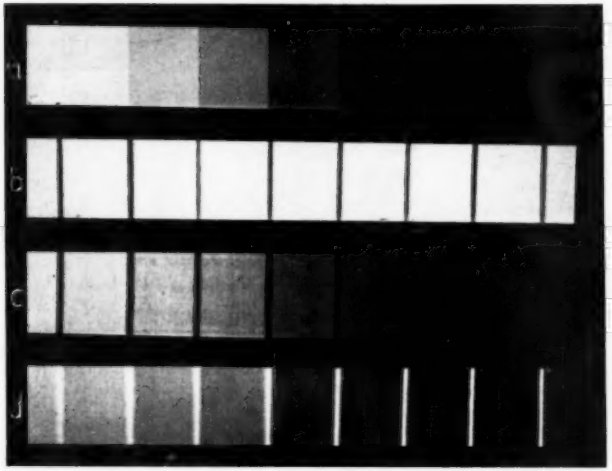

Fig. 4. a) Staircase exposure. b) Gradient image. c) Crispening image. d) Isogradient image with unexposed traces.

in the surface scanned by the rotating light spot. This is accomplished through a d. c. feedback amplifier between the multiplier and the incandescent lamp. The amplifier has a time constant that is large compared with the period of rotation of the light spot. The gain is 60 dB. This makes the average transmitted light intensity essentially constant for film density values between 0 and 3.

The a. c. component of the multiplier current becomes proportional to the absolute value of the density gradient, as described above, since the factor $1/T$ in the equation is taken care of by the feedback circuit. The gradient voltage, with the same frequency as the rotating light spot, is amplified in a tuned amplifier in order to increase the signal to noise ratio. After logarithmic amplification with a transfer function that can be chosen with a 'gamma selector', the gradient voltage is rectified. The gradient voltage exercises control over the light output of the glow modulator tube.

The light output from the glow modulator tube must be made proportional to a control voltage. This is done by a pulse repetition-frequency system. The glow modulator is fed with pulses of constant length and amplitude but with varying frequency. Since the frequency is proportional to the input voltage the same holds for the average light output.

The three methods for transforming the image are indicated by the switch positions in Fig. 3. Fig. 4 gives the images obtained from a

staircase exposure. In the first method the gradient voltage itself constitutes the control voltage for the glow modulator tube. Thus the exposure becomes proportional to the image gradient. The resultant gradient image contains only the contours of the details of the original image. By logarithmic amplification weak density differences can be amplified relatively more than large differences.

The second method is similar to the crispening technique used in television systems (FINK 1951). The glow modulator circuit is fed with a mixed control voltage. One part of the voltage is inversely proportional to the average transmission in the image element (the area scanned by the rotating light spot). This voltage is obtained from a vacuum phototube placed near the incandescent lamp. The other part of the voltage is proportional to a logarithmic function of the gradient. The new image resembles the original one but has reinforced contours where the original has density gradients.

In the third method the glow modulator circuit is fed with a voltage inversely proportional to the average transmission in the image element. The recorded density becomes approximately equal in the two films; in addition the recorded image contains unexposed or overexposed traces joining points of equal density gradient. This is done by a ten-channel amplitude discriminator which actuates two relays each time the gradient voltage falls within certain pre-set levels. The relays either block or intensify the glow modulator output. The isogradients in the recorded image are arbitrarily chosen to be overexposed or underexposed. This facilitates the recognition of certain gradient levels which process is of importance for quantitative determinations. In Fig. 4 d the discriminator was adjusted to obtain unexposed traces for all gradient levels in the original image.

Sensitivity of the method

The sensitivity of the method is determined by the signal-to-noise ratio of the gradient voltage and by the mechanical and electrical stability of the apparatus. A too high selectivity of the tuned amplifier makes the response time of the recording unit very large and necessitates a slow scanning speed. Fortunately, high sensitivity is possible even with a modest selectivity. With a rise time of 0.2 seconds and a 25 c/s gradient signal frequency, a sensitivity can be obtained permitting the recording of transmission differences of 0.01 per cent. The finite response time causes the gradient lines in Fig. 4 to have a zigzag structure.

The sensitivity of the method is far beyond what can be utilized with present standard films. Noise occurs due to several factors in the original image. Graininess, varying thickness of the emulsion layer,

shadows due to dust, and non-uniform processing defects are of importance.

With increasing size of the rotating light spot the noise decreases. Even if the light spot has a diameter of 0.2 cm the noise for commercial roentgen films has a level that corresponds to a difference of 0.01 to 0.0003 density units. Since different photographic films vary considerably in this respect, it is likely that much can be done in order to improve on the property of uniformity. Still, a sensitivity corresponding to a density difference of 0.0003 units is almost ten times as much as the human eye can see. Moreover, it should be noted that the density range for resolving small contrasts is more limited for the human eye than for the image transforming photometer which, due to the feedback circuit, works in the range from 0 to over 3. Furthermore, to be observable to the eye, a sharp gradient is needed within a small area, whereas the photometer can detect a continuous gradient over the whole area scanned by the rotating light spot.

Applicability of the method

The method might find applications in various fields of photography such as testing the quality of photographic materials and film spectroscopy for resolving weak or overlapping lines. In medical and industrial radiography the method can be employed for observing weak contrasts; especially in connection with tomography and soft tissue radiography where large contrasts are absent, advantage should be obtained from image transformations. The limiting factor of the method essentially lies in the properties of the emulsion layer as is demonstrated in Fig. 5.

Fig. 5a shows an ordinary radiograph of a phantom consisting of 500 sheets of bond paper with 50 additional sheets having cut-out regions. In Fig. 5b the fractional mass difference is given that exists at the various contours. The radiograph was taken on a fine grain industrial roentgen film with 60 kV and an exposure time continuously varying from 100 mAs on the upper edge of the radiograph to 300 mAs at the lower edge. This was achieved by moving a lead shield at a constant speed in such a way that an increasing part of the phantom was shadowed during the exposure.

Fig. 5c shows a gradient image of the radiograph in (a). More details can be seen in the gradient image than in the original. Due to the feedback circuit the varying density level of the original radiograph does not prevent the detection of weak gradients in either the weakly or heavily exposed areas. The more exposed areas in the upper left half of the gradient image, representing larger noise levels, are largely due to two factors. For one thing, lower density levels, as present in

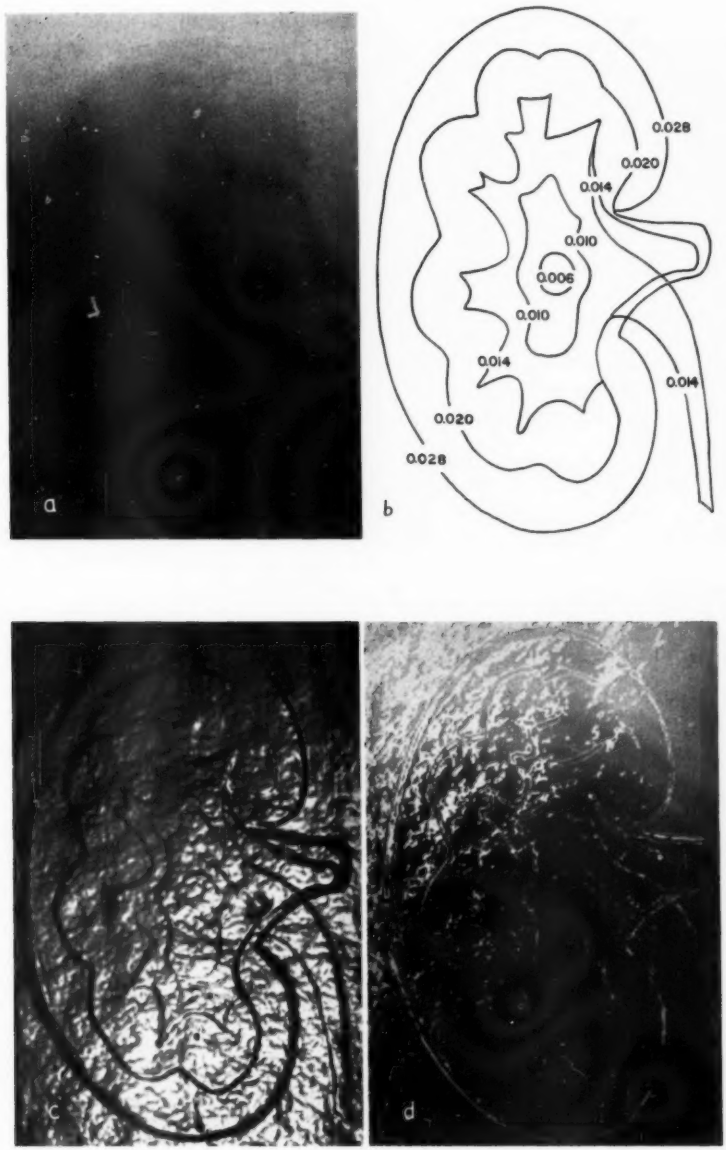

Fig. 5. a) Ordinary radiograph of a phantom. b) Fractional mass differences existing at the various contours. c) Gradient image. d) Isogradient image.

the upper part of the original radiograph, in general give higher noise levels since there are fewer developed grains to average out statistical fluctuations. Secondly, the thickness of the emulsion layer of the original radiograph varies along the left edge of the image and causes a gradient image which contains a darker shaded area to the left. The general mottled appearance of the gradient image is due to uneven thickness of the emulsion layer and such local fluctuations actually place the practical limitation on the power of the method to resolve density gradients.

Fig. 5d shows the isogradient image of the radiograph. The large noise level in the upper left section of the radiograph is evident. It should be observed that the density at each point, except for the isogradients, is essentially the same as in the original radiograph. Although not of particular significance in the image shown, this might be of value for recognizing involved structural details in other images.

SUMMARY

A scanning instrument for the transformation of an image of an original film into a new image in order to render small density differences visible is described. The major limiting factor of the method lies in the uneven emulsion thickness of commercially available films. The method might find applications in radiography for observing weak contrasts and in certain fields of photography.

ZUSAMMENFASSUNG

Ein Instrumentarium zur Überführung des Bildes eines Originalfilmes in ein neues Bild, um kleine Schwärzungsdifferenzen sichtbar zu machen, wird beschrieben. Die wesentlichste Beschränkung der Methode liegt in der ungleichförmigen Emulsionsdicke der im Handel zugänglichen Filme. Die Methode kann in der Radiographie zur Beobachtung weicher Kontraste sowie in gewissen Gebieten der Photographie zur Anwendung kommen.

RÉSUMÉ

L'auteur décrit un appareil permettant de transformer l'image d'un film original en une nouvelle image, de façon à rendre visibles de petites différences de densité. Le principal facteur limitant les possibilités de cette méthode est l'irrégularité de l'épaisseur de l'émulsion des films du commerce. Cette méthode pourrait trouver des applications en radiographie pour l'observation de faibles contrastes, et dans certaines utilisations de la photographie.

REFERENCE

FINK, D. G.: Crispening circuit for color TV. Electronics 24 (1951): 9, p. 85.

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STUDIES ON RADIOACTIVE SULPHUR S^{35} PRECIPITATED IN BENZIDINE SULPHATE

I. A method of preparing solid samples and measurement of the self-absorption curve

by

Erik Ågren

In order to measure the relative activity in organic and inorganic sources containing radioactive sulphur S^{35} it is sometimes convenient to change the latter into solid measuring samples. The activity in the samples may then be measured in a Geiger counter with a thin mica end-window (< 2 mg/cm^2).

To achieve sufficient accuracy in the measurements the solid samples must be prepared in such a way that the radioactive sulphur is uniformly distributed and in the same chemical form. The samples must also be smooth and even and of the same area, and the sulphur must be precipitated on the same material in each case. The same elementary mounting must also be used to eliminate deviations due to difference in secondary radiation and back-scattering. In the preparation of the samples every care must of course be taken to avoid any loss of activity.

Submitted for publication 27 May 1957.

Various methods of producing solid samples have been described (HENRIQUES et coll. 1946, ARMSTRONG and SCHUBERT 1948). As it proved difficult in our experiments to produce solid samples with sufficient accuracy according to these methods we finally worked out a modified procedure.

The sulphur in the samples was oxidized to sulphate by a special method. The sulphate was then precipitated as benzidine sulphate. Much care was taken to avoid impurities in the precipitates, as even slight impurities may cause absorption losses. Methods of precipitating the sulphur as barium sulphate may also be found in the literature.

However, benzidine hydrochloride is considered a better sulphate precipitant than barium chloride, as it gives more uniform precipitates (HENRIQUES et coll. 1946 and KAMEN 1951). In our attempts to compare barium and benzidine sulphate precipitates in the way set out below, it proved impossible to obtain reproducible samples with barium chloride. The method used has therefore been to precipitate the sulphur in the samples as benzidine sulphate. A simple way of doing this is to start with a sodium sulphate solution.

Method of preparing solid samples

A known sodium sulphate solution was prepared, 2 ml of which when precipitated by 2 ml of benzidine hydrochloride prepared according to NIEDERL et coll. 1940, gave 10 mg of benzidine sulphate. With the aid of a burette, increasing quantities of the sulphate solution were poured into 14 beakers, and a fixed equal amount of radioactive sulphur, supplied by the Radiochemical Centre, Amersham, England (sulphur 35, carrier-free sulphate in aqueous solution pH 7) was added to each beaker. After adjusting the pH of the solutions with phenolphtalein 2N·NaOH and N·HCl to a suitable value for the precipitation of benzidine sulphate (about 6 to 7), benzidine hydrochloride was added. Fourteen different precipitations were thus obtained and subsequently made into solid samples, from which a series of samples varying by about 5 mg/cm² from 0.8 to 63.4 mg/cm² were prepared.

The following equipment (Fig. 1) was used in the experiments:

A disc (FPM) 23.5 mm in diameter was punched from Munktell filter-paper, Mark OK, weighed and placed on a glass filter of known porosity, (GF) G² (supplied by Pyrex, France). This glass filter was mounted in the opening of a glass funnel forming part of an ordinary suction filter device (S). A glass cylinder (GC) with an internal diameter of 19.1 mm, and fitting closely to the filter, was held firmly to this by coil springs. Strong regular suction was applied, and the benzidine sulphate solution poured quickly into the glass cylinder from the beaker. When the solution had

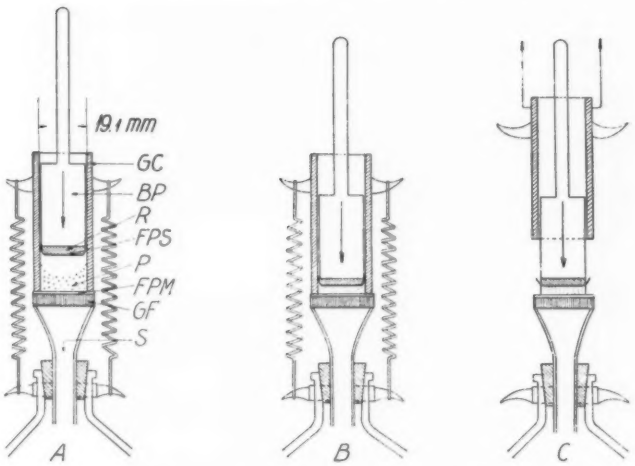
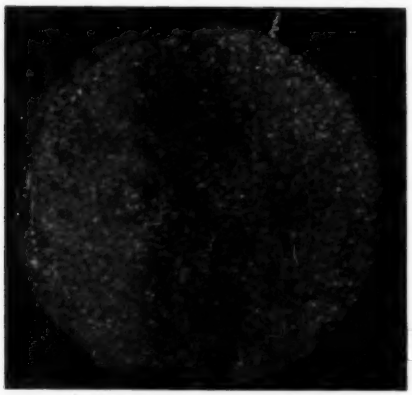


Fig. 1. Equipment for preparing solid samples containing radioactive sulphur S^{35}.

passed through the filter, both beaker and cylinder were carefully washed with small amounts of absolute alcohol (total volume 10 ml). The apparatus is similar to that described by TARVER and SCHMIDT 1939 and HENRIQUES et coll. 1946.

The precipitate (P) was thus collected on the filter paper, but in order also to transfer to the filter the portion which still adhered to the lower part of the wall of the glass cylinder a brass piston (BP), the end of which was covered with rubber (R), was used to press it down. It was found, however, that small particles of the precipitate adhered to the rubber packing of the piston; in order to overcome this difficulty another filter paper disc slightly larger in diameter than the piston was punched out and held on the packing by a few drops of water. After the precipitate had been compressed in this manner with the piston, first the cylinder and then the piston were carefully removed. The filter paper (FPS) now adhered to the precipitate and had to be removed in the following manner. Alcohol and ether were dropped on the filter paper which was then warmed with an evaporating lamp for 3 to 5 minutes. Then the water pump was turned off and the paper could easily be loosened from the precipitate without anything adhering to it. It was possible in this way to obtain smooth tablets of the precipitate on the filter paper. They usually adhere firmly to the filter paper (Fig. 2 a) and the radioactive substance is always uniformly dispersed. To avoid damage to the tablets when counting, the filter papers were placed in aluminium planchets

a



b

Fig. 2. a) Radioactive sulphur S^{35} precipitated as benzidine sulphate. Reproduction 1:1. The precipitate in the aluminium planchet is precipitated on Munktell's filter paper, Mark OK, and usually adheres firmly to the paper. In thicknesses ≥ 2 mg the strength of the precipitates is sufficient to allow of their removal from the paper. b) One of the precipitates in (a). Magnification 3: 1. The surface is smooth and even on inspection.

into which they fitted exactly. The weight of the precipitates could then be determined within $\pm$ 0.1 mg.

The evenness and smoothness of the sample surfaces were checked visually (Fig. 2) and by microscopical inspection. The criterion adopted for judging these qualities was that it should be possible to see clearly the whole surface of the precipitate, from top to bottom without having to alter the focussing of the microscope. The measurements were made with a binocular microscope using a magnification of 800. The focal depth of the objective was 10 μ.

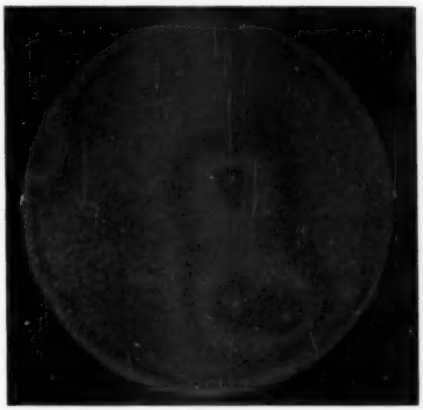


Fig. 3. Autoradiogram of a benzidine sulphate precipitate, indicating uniform dispersion of S^{35}. Magnification 3:1. Blue Brand Ultra Speed Kodak X-Ray Film. Exposure time: 48 hours.

The dispersion of the radioactive compound was checked by radiography (Fig. 3) and in the following manner.

An acrylic ring fitting the sample exactly was fixed below the window of a Geiger tube. The right half of the sample was first covered by a lead absorber, and the radiation from the left half was counted. After moving the absorber over to the left half the radiation from the right half was in its turn counted, and finally the ratio between the two halves was computed. A ratio of 1 would of course indicate perfect dispersion.

This experiment was performed on thin samples (1.92 to 2.20 mg/cm²) and also on thicker samples (8.67 to 8.81 mg/cm²). (Tables 1 and 2.)

The method described above can be used to identify radioactive sulphur in organic as well as inorganic compounds. Organic substances must therefore first be completely incinerated before the sulphur in the samples can be precipitated. A special incinerating method has accordingly been worked out, an account of which will be published separately.

Table 1

Check of the uniform distribution of S^{35} in the samples. All counts are averages of triple observations

Sample	Weight mg/cm²	Total activity counts/min.	Activity		Left/Right Ratio
			Left half counts/min.	Right half counts/min.	
1	1.92	18,392	11,652	11,569	1.01
2	2.20	15,911	9,505	9,909	0.96
3	2.20	16,001	9,479	9,717	0.98
4	2.20	16,241	9,572	10,036	0.95
5	2.17	16,284	9,869	9,829	1.00

Table 2

Check of the uniform distribution of S^{35} in the samples. All counts are averages of triple observations

Sample	Weight mg/cm²	Total activity counts/min.	Activity Left half counts/min.	Activity Right half counts/min.	Left/Right Ratio
1	8.77	4,095	2,230	2,182	1.02
2	8.67	4,000	2,165	2,216	0.96
3	8.70	3,858	2,128	2,135	1.00
4	8.67	3,896	2,175	2,256	0.96
5	8.81	3,859	2,109	2,243	0.94

The following experiment has been made to illustrate: (1) the accuracy with which radioactive sulphur, added to organic compounds, can be recovered, and (2) the possibility of obtaining solid samples of identical weights and activities.

A quantity of urine was divided into ten samples of 3 ml each. A quantity of S^{35}, the same in each case, was pipetted into each sample. The weight of the radioactive sulphur may be disregarded. After the samples had been incinerated in the special manner referred to, the sulphur in the urine was precipitated as described above. The results are given in Table 3.

Table 3

Recovery of S^{35} from incinerated urine samples containing a given amount of S^{35} and the accuracy of making solid samples as regards weights and activities

Urine sample	Benzidine-sulphate precipitate weight in mg	Counts/min.
1	7.2	10,930
2	7.7	10,871
3	7.2	11,081
4	7.4	10,930
5	7.3	11,050
6	7.7	10,832
7	7.5	10,989
8	7.7	10,870
9	7.3	11,111
10	7.2	10,812
Mean	7.42 mg	10,947 counts/min.
Standard deviation	0.21 mg	106 counts/min.
Coefficient of variation	2.83 %	0.96 %

The precision which can be attained by measurements in a Geiger counter is limited by the statistical accuracy of the counting. Every measurement is impaired by an error due to the fact that the emission of beta-particles in the samples is statistically distributed in time. For strong samples this 'statistical error' can be computed by taking the

square root of the number of counts observed. The mean of these errors amounted to 105 counts/min., or about 1 per cent, in the ten urine samples. According to Table 3 the standard deviation of the activity is 106 counts/min., *i. e.*, a figure almost equal to the mean statistical error. The coefficient of variation was 0.96 per cent.

This method thus makes it possible to produce from organic compounds benzidine sulphate precipitations of reproducible activity. The fact that the net activity of every evaporated quantity of the supernatant liquid, obtained after filtering and washing the precipitates was only 32 counts/min. (mean results of five experiments, background 26 counts/min.) justifies the assumption that this method allows the determination of radioactive sulphur in benzidine precipitates without appreciable loss. Account must, however, be taken of the possibility that not all the S^{35} pipetted to the samples is precipitated. As regards the possibility of obtaining from the same material benzidine sulphate precipitates of identical thicknesses (mg/cm²), the margin of error is 2.83 per cent.

The results of this method of precipitating S^{35} as benzidine sulphate are reproducible, and the activities of both thin and thick precipitates can accordingly be determined. Their accuracy is sufficient for plotting a curve showing the self-absorption of S^{35} in benzidine sulphate in solid samples produced by the method described above. This procedure is described in the following. Owing to the low energy of beta rays from S^{35}, all counts of beta rays from this radioisotope must be corrected for self-absorption unless 'carrier-free' samples are used. The self-absorption values of this isotope precipitated as benzidine sulphate have been studied by HENRIQUES et coll., 1946. They gave corresponding weight correction factors for the self-absorption of S^{35} beta particles in benzidine sulphate layers between 0.46 to 11.60 mg/cm². The precipitates were collected on Munktell filter paper, Mark OK, and measured by a Geiger tube.

LIBBY 1947 gives empirical equations of the absorption in solid samples emitting soft beta rays. The self-absorption curve of benzidine sulphate (S^{35}) samples of up to 35 mg/cm² has been studied by GLENDENIN and SOLOMON 1950. Using aluminium (atomic number 13) and beryllium (atomic number 4) dishes, they found that back-scattering increasing with the atomic number of the dish metal could only be observed in samples of less than 6 mg/cm². If the samples were thicker the atomic number of the dish metal had no effect on the self-absorption curve. They also found that the self-scattering of the sample increased with the mean atomic number of the sample material.

It therefore seems advisable that self-absorption curves should be plotted under the particular conditions obtaining in each experiment. In these experiments, moreover, tests covering a greater range than before have been made.

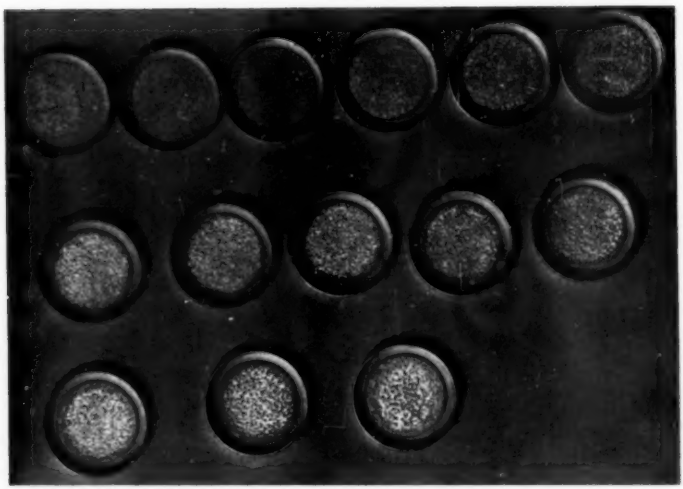


Fig. 4. The samples used for constructing the self-absorption curve of S^{35} in benzidine sulphate. The upper precipitate to the left weighs 0.8 mg/cm², that to the right below 63.42 mg/cm².

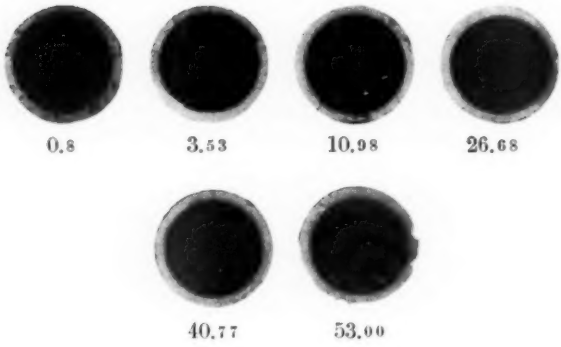


Fig. 5. Autoradiograms of some of the samples in fig. 4 with decreasing radioactivity. The numerals refer to the thickness of the samples. The uniform blacking of the autoradiograms indicates uniformity of the radioactivity of the samples.

Measurement of the self-absorption curve

Using the method described in the foregoing for the preparation of the samples of benzidine sulphate containing S^{35}, the self-absorption of these was studied experimentally. All the samples contained equal quantities of S^{35} in varying amounts of benzidine sulphate. The samples varied in thickness from 0.8 to 62.4 mg/cm². Good quality samples could not be prepared thinner than 0.8 mg/cm².

The activity of the precipitates was measured with a Tracerlab end-window tube TGC-2 with a window 1.8 mg/cm² thick and effective diameter 27.5 cm. The tube was combined with a Philips Electronic counter PW 4,032. This counter had a threshold at about 1,325 volts. The characteristic plateau curve of the Geiger tube was checked for constancy. Its slope was less than 2 per cent and its length 300 volts. The vertical distance from the sample to the counter window was 17 mm. The diameter of the precipitate on Munktell's filter paper was 19.1 mm over an area of 2.86 cm². The aluminium dishes were 0.5 cm deep and 0.045 cm thick. They were supported on a shelf with devices for holding the dishes in exactly the same positions every time, thus always ensuring correct positioning of the samples under the Geiger tube.

The autoscaler was set for 10,000 counts, and its margin of error was 1 per cent. Background was determined with an aluminium dish with filter paper. When checking the background rate the count selector was set for 4,000 counts. The background rate was about 38 counts/min. and remained constant throughout the measurements. Correction was made for the effective resolving time of the equipment, which was found to be 220 μ sec.

While the samples were being counted, the humidity of the air in the room was kept constant. A rise in humidity would by increasing the self-absorption cause a gradual decrease in the count of the sample. Constant humidity in the samples during the count was ensured by allowing them to remain outside the Geiger tube for 40 minutes in unstoppered weighing bottles. It was proved experimentally that the samples had in that time absorbed the humidity necessary to ensure that no variation in the counts due to increased self-absorption occurred.

The counting rates were plotted against sample thicknesses (Diagram 1). A correction chart (Table 4) was obtained from the self-absorption curve.

The accuracy of the results is influenced not only by the statistical fluctuations of the counts, but also by other factors. Uniformity in the samples is an important factor. This was as mentioned before checked by separate experiments, and inspection: visually, by microscopy and autoradiography. The quality of the samples was found to be acceptable, as indicated in Figs. 4 and 5.

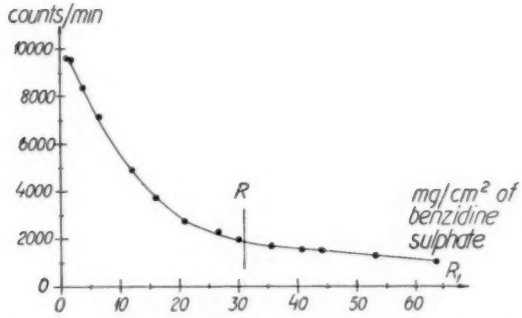


Diagram 1. Self-absorption curve of S^{35} in benzidine sulphate. Maximum range (infinite thickness) at about 31 mg/cm².

Differences in absorption in the air column between the sample and the Geiger tube, due to variations in atmospheric pressure, temperature and humidity, are other sources of error. Rough calculations and experiments show that these errors are comparatively small.

An interpretation of the results will be given in a following paper.

Table 4

Self-absorption correction factors for varying thicknesses of S^{35} in benzidine sulphate

Total weight of benzidine sulphate precipitate in mg	Weight of precipitate mg/cm²	Self-absorption correction factor[1]
2.3	0.8	0.965
4.4	1.54	0.950
10.1	3.53	0.840
15.2	5.31	0.725
31.4	10.98	0.498
46.0	16.08	0.375
60.5	21.15	0.275
76.3	26.68	0.230
86.2	30.14	0.205
101.5	35.49	0.175
116.6	40.77	0.158
126.0	44.06	0.148
151.6	53.0	0.125
181.4	63.42	0.105

[1] The net activity is to be divided by this factor.

Acknowledgements

The experiments have been carried out at the Clinical Laboratory of the Royal School of Dentistry in Stockholm, and at the Isotope Laboratory of the Department of Obstetrics and Gynaecology, Karolinska Institutet, Sabbatsbergs Sjukhus, Stockholm. The author's thanks are due to Professor YNGVE ERICSSON and Docent ERIK ODEBLAD for the helpful advice given him throughout the work, and to Mr. CARL ÅBORG for his skilful assistance. Financial support for this investigation was provided by the Swedish Medical Research Council and the Swedish Dental Association.

SUMMARY

A method is described for preparing solid measuring-samples containing radioactive sulphur S^{35} in benzidine sulphate, the activity of which may then be measured in a Geiger counter. Samples which could be used as a basis for the experimental construction of a self-absorption curve for S^{35} have been produced. The self-absorption of the beta-radiation of this isotope is shown in a curve, where the observed activity is plotted against sample thickness. Self-absorption correction factors for varying thicknesses are given. An interpretation of the results is published in the immediately following article.

ZUSAMMENFASSUNG

Eine Methode zur Bereitung von solidem Untersuchungsmaterial, welches in Benzidinsulphat gelösten radioaktiven Schwefel, S^{35}, enthält, wird beschrieben. Die Aktivität der Probe kann dann mit einem Geigerzähler gemessen werden. Solide Probestücken wurden hergestellt und die Eigenabsorption der Betastrahlung dieses Isotopen wird in einer Kurve gezeigt, in der die beobachtete Aktivität im Verhältnis zur Dicke der Proben dargestellt ist. Korrektionsfaktoren für die Eigenabsorption bei verschiedenen Dicken werden angegeben. Eine Auslegung der Resultate ist im nächstfolgenden Artikel publiziert.

RÉSUMÉ

L'auteur décrit une méthode de préparation d'échantillons de mesure solides contenant du soufre radioactif S^{35} dans du sulfate de benzidine, dont on peut ainsi mesurer l'activité avec un compteur de Geiger. Des échantillons solides de sulfate de benzidine contenant du S^{35} ont été préparés et leur auto-absorption a été étudiée expérimentalement. L'auto-absorption du rayonnement bêta de cet isotope est figurée par une courbe ou l'activité observée est représentée en fonction de l'épaisseur de l'échantillon; des facteurs de correction d'auto-absorption sont indiqués pour différentes épaisseurs. Une interprétation des résultats est publiée dans l'article suivant.

REFERENCES

ARMSTRONG, W. D. and SCHUBERT, J.: Determination of radioactive carbon in solid samples. Anal. Chem. 20 (1948), 270.

GLENDENIN, L. E. and SOLOMON, A. K.: Self-absorption and back-scattering of β-radiation. Science 112 (1950), 623.

HENRIQUES, JR, F. C., KRISTIAKOWSKY, G. B., MARGNETTI, CH. and SCHNEIDER, W. G.: Radioactive studies. Analytical procedure for measurement of long-lived radioactive sulphur, S^{35}, with a Lauritzen electroscope and comparison of electroscope with special Geiger counter. Ind. Eng. Chem. Anal. Edit. 18 (1946), 349.

KAMEN, M. D.: Radioactive tracers in biology. Academic Press, Newyork 1951.

LIBBY, W. F.: Measurement of radioactive tracers, particularly C^{14}, S^{35}, T, and other longer-lived low-energy activities. Anal. Chem. 19 (1947), 2.

NIEDERL, J. B., BAUM, H., MC COY, J. S. and KUCK, J. A.: Micro-Carius halogen and sulphur determination. Ind. Eng. Chem. Anal. Edit. 12 (1940), 428.

TARVER, H. and SCHMIDT, C. L. A.: The conversion of methionine to cystine. J. Biol. Chem. 130 (1939), 67.

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STUDIES ON RADIOACTIVE SULPHUR S^{35} PRECIPITATED IN BENZIDINE SULPHATE

II. An interpretation of the self-absorption curve

by

Erik Ågren and *Erik Odeblad*

It is of considerable interest to find a theoretical explanation for the experimental results obtained in a preceding paper (ÅGREN 1957). Within a certain range of the experimental curve, that is from a few mg/cm² up to the maximum range, R, of about 31 mg/cm² (GLENDENIN and SOLOMON 1950), it is possible to obtain an analytical expression in the following way. Starting from the binominal formula for beta-ray transmission (ODEBLAD 1955) we can write the following equation for the counting rate, c, for a layer of thickness dr:

$$c\,dr = BMG\left(1 - \frac{r}{R}\right)^n dr \quad \ldots\ldots\ldots\ldots\ldots \quad (1)$$

Here M is the amount of radio-isotope (S^{35}) in disintegrations per unit time, G the geometry factor, and B the back-scattering factor. The window transmission is put equal to unity. Integration between 0 and R_1 yields

$$c = BMG \int_0^{R_1} \left(1 - \frac{r}{R}\right)^n dr \Big/ \int_0^{R_1} dr \quad \ldots\ldots\ldots\ldots\ldots \quad (2)$$

Submitted for publication 27 May 1957.

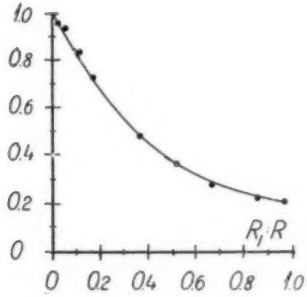

Diagram 1. Experimental data and theoretical self-absorption curve in the range $R_1 < R$. The back-scattering factor B is assumed to be constant in the theoretical calculations.

Since the radioactive benzidine sulphate, having the average atomic number 4.6, was plated on paper with an average atomic number 4.1, we could expect the factor B on the average not to be quite constant but to increase slightly in the first portion of the self-absorption curve. Evaluating the integral in eq. (2), if $n = 4$ (as is indicated by recent work, viz. ODEBLAD 1955, 1957) we obtain

$$c = BMG\ (1 - 2x + 2x^2 - x^3 + x^4/5) \quad \ldots\ldots\ldots\ldots \quad (3)$$

where $x = R_1/R$. In diagram 1, this relation is compared with the experimental data of ÅGREN 1957.

Equation (3) is valid only if $R_1 < R$. If $R_1 > R$ this will have the effect of 'diluting' the sample with a factor R/R_1, so for this part of the self-absorption curve we can write

$$c = BMG\ R/nR_1 \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (4)$$

Eq. (4) can be put in logarithmic form as follows:

$$\log c = \log (BMGR/4) - \log R_1 \ldots\ldots\ldots\ldots \quad (5)$$

Equation (4) means that beyond R there should be a straight line relation between counting rate and sample thickness in a double-logarithmic plot. In Diagram 2 the experimental data obtained by ÅGREN 1957 are compared with eq. (4).

In order to elucidate the back-scattering effect of various backing materials on the first portion of the curve, we plated benzidine-S^{35}-sulphate of same thicknesses on different holders. The results are shown in Diagram 3. Similar results were reported by GLENDENIN and SOLOMON 1950, who used different materials for mounting the samples.

The present analysis indicates that the self-absorption curve of benzidine-S^{35}-sulphate in principle can be divided into three parts, viz. a

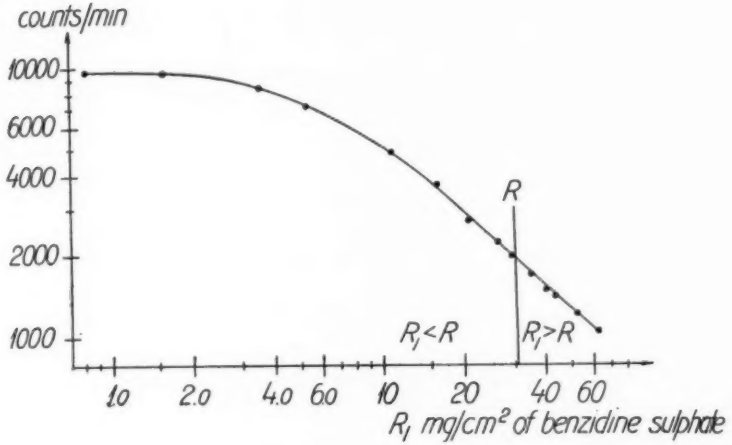

Diagram 2. Experimental data and theoretical self-absorption curve for $R_1 > R$.

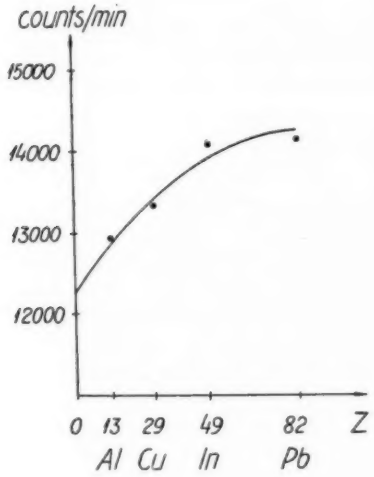

Diagram 3. Influence of different backing materials on the early portion of the self-absorption curve.

middle portion governed by the effect of increased self-absorption, an *early* portion where the back-scattering from the backing material also comes into play, and a *third* portion where 'dilution' of the sample governs the course of the curve. There is good reason to believe that these parts of the curve may to a greater or lesser extent be recognized in any self-absorption curve.

SUMMARY

A theoretical analysis compared with experimental data indicates that the self-absorption curve of benzidine-S^{35}-sulphate consists of three portions governed by different mechanisms in the establishment of the counting rate.

ZUSAMMENFASSUNG

Der Vergleich einer theoretischen Analyse mit experimentellen Daten zeigt, dass die Eigenabsorptionskurve des in Benzidinsulphat gelösten radioaktiven Schwefels (S^{35}) aus 3 Abschnitte besteht. Diese werden von verschiedenartigen Mechanismen bei der Feststellung der Messgeschwindigkeit beherrscht.

RÉSUMÉ

L'analyse théorique comparée aux données expérimentales indique que la courbe d'auto-absorption du sulfate S^{35} de benzidine comporte trois portions régiés par des mécanismes différents intervenant dans l'établissement du taux de comptage.

REFERENCES

GLENDENIN, L. E. and SOLOMON, A. K.: Self-absorption and back-scattering of β radiation. Science 112 (1950), 623.

ODEBLAD, E.: Approximate formula describing transmission and absorption of beta-rays. Acta radiol. 43 (1955), 310.

— Further approximate studies on beta-ray transmission and absorption. Acta radiol. 48 (1957), 289.

ÅGREN, E.: Studies on radioactive sulphur S^{35} precipitated in benzidine sulphate. I. A method of preparing solid samples and measurement of the self-absorption curve. Acta radiol. 48 (1957), 385.